FORMULATION AND EVALUATION OF FEXOFENADINE HYDROCHLORIDE FILM COATED TABLETS

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Submitted by

C.REVATHY

(Register No: 26114510)

Under the Guidance of

Prof. Mrs. RAJARAJESWARI HARIHARAN, M.Pharm.,

DEPARTMENT OF PHARMACEUTICS

K.K. COLLEGE OF PHARMACY

GERUGAMBAKKAM, CHENNAI - 600122

APRIL-2013

CERTIFICATE

This is to Certify that the dissertation entitled **"FORMULATION AND EVALUATION OF FEXOFENADINE HYDROCHLORIDE FILM COATED TABLETS"** is a bonafide and genuine research work carried out by **Miss. C.REVATHY,** during the academic year 2012-2013 under the supervision of **Mrs. RAJARAJESWARI HARIHARAN, M.Pharm.,** Professor, Department of Pharmaceutics, K.K. College of Pharmacy, Chennai - 600122. This dissertation submitted in partial fulfilment for the award of degree of **Master of Pharmacy (Pharmaceutics)** by The Tamil Nadu Dr. M.G.R Medical University, Chennai – 32.

Prof. A.Meena, M.Pharm, (Ph.D),
Principal
K.K. College of Pharmacy
Chennai 600122

Prof. Dr.V.Vaidhyalingam, M.Pharm Ph.D
Director
K.K. College of Pharmacy
Chennai 600122

CERTIFICATE

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Prof. Dr.K.Senthilkumaran M.Pharm., Ph.D.,
Head of Department
Department of Pharmaceutics
K.K.College of Pharmacy
Chennai - 60012

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Guide
Mrs. Rajarajeswari Hariharan M.Pharm.,
Professor,
Department of Pharmaceutics,
K.K.College of Pharmacy,
Chennai – 60012.

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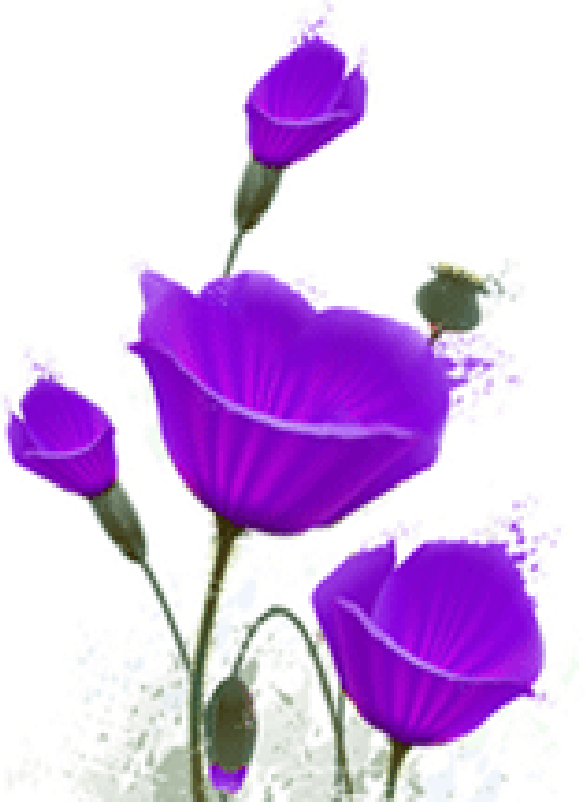

Dedicated to

God, my parents & our beloved faculty members

ABBREVATIONS

^{o}C	-	Degree centigrade
α	-	Alpha
β	-	Beta
≠	-	sieve number
API	-	Active Pharmaceutical Ingredients
AUC	-	Area Under Curve
BP	-	British Pharmacopeia
CAP	-	Cellulose Acetate phthalate
cm	-	centimeter
D&C	-	Drug and Cosmetics
DT	-	Disintegration Time
FDA	-	Food and Drug Administration
FDC	-	Federal food Drug & Cosmetics act
FTIR	-	Fourier Transform Infrared Spectroscopy
GMP	-	Good Manufacturing Practice
GIT	-	Gastro Intestinal tract
HPMC	-	Hydroxyl Propyl Methyl Cellulose
HPC	-	Hydroxyl Propyl Cellulose
HPLC	-	High Performance Liquid Chromatography
Hrs	-	Hours
JP	-	Japanese Pharmacopeia
KBr	-	Potassium Bromide
Kg/Cm^2	-	Kilogram per Centimeter square
LOD	-	Loss On Drying
MCC	-	Micro Crystalline Cellulose
mg	-	milligram

mg/ml	-	milligram/millilitre
Mg	-	Magnesium
µl	-	microlitre
µm	-	micrometer
µg	-	microgram
µg/ml	-	microgram per millilitre
mg/tab	-	milligram per tablet
N	-	Normality
nm	-	nanometer
g/ml	-	Gram per ml
NLT	-	Not Less Than
NMT	-	Not More Than
PEG	-	Poly Ethylene Glycol
PVP	-	Poly Vinyl Pyrolidone
PhEur	-	European Pharmacopeia
RH	-	Relative Humidity
Rpm	-	Revolution per minute
SD	-	Standard Deviation
$T_{1/2}$	-	Half life
USP	-	United Stated Pharmacopeia
USP NF	-	United Stated Pharmacopeia National Formulary
UV	-	Ultraviolet Visible
W/V	-	Weight per Volume

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I. INTRODUCTION[1]

The oral route of drug administration is the most important method of administrating drugs for systemic effects. Oral drug delivery has been known for decades as the most widely utilized route among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration, belief that by oral administration of the drug is well absorbed.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion (or) liquid), must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodynamics and formulation design to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.

1.1 TABLETS

Tablets are solid dosage forms each containing a unit dose of one or more medicaments. They are intended for oral administration. Some tablets are swallowed whole or after being chewed, some are dissolved or dispersed in water before administration and some are retained in the mouth where the active ingredient is liberated.

Tablets are used mainly for systemic drug delivery but also for local drug action. For systemic use, the drug must release from the tablet by normally dissolving in the fluids of the mouth, stomach or intestine and thereafter be absorbed into the systemic circulation. Because of their composition, method of manufacture or intended use, tablets present a variety of characteristics and consequently there are several categories of tablets.

Tablets are usually solid, right circular cylinders, the end surfaces of which are flat or convex and the edges of which may be beveled. They may exist in other shapes like triangular, rectangular, etc also. They may have lines or break-marks and may bear a symbol or other markings. They are sufficiently hard to withstand handling without crumbling or breaking.

TABLET PROPERTIES

- Tablet should be elegant product having its own identity while being free of defects such as capping, cracks, discoloration and any other contamination.
- Tablets should have the strength to withstand the rigors of mechanical shocks encountered in its production, packaging, shipping, dispensing and handling.
- Tablets should have chemical and physical stability to maintain its physical attributes over time.
- Tablets should be able to release the active ingredient in the body in a predictable and reproducible manner.
- Tablets must have a suitable chemical stability over time so as not to allow any degradation or alteration of the active moiety.

ADVANTAGES OF TABLETS

- Tablet is orally administered non invasive unit dosage form, and also has the greatest dose precision when self medication is considered which makes it the most popular formulation among the patients.
- They may provide the greatest ease of swallowing with the least tendency for "hang – up" above the stomach, especially when coated, provided that tablet disintegration is not excessively rapid.
- Tablets are the easiest and most economical to pack and ship as compared to other oral dosage forms.
- Product identification is simple by using punches of different shapes or some embossing on the punches.
- Tablets are better suited for large- scale production than other unit dosage forms.
- Tablets lend themselves to certain special release profile products. Such as enteric or delayed release products.

- ❖ Tablets have the best - combined properties of chemical, mechanical and microbiological stability as compared to other oral forms.
- ❖ Tablets are the maximum profit making when reviewed through pharmaceutical company' perspective.

DISADVANTAGES OF TABLETS:

- ❖ When the dose of the drug is large, tablets might be too big for children or even adults to swallow.
- ❖ When the drugs need to act very fast, the disintegration of the tablet and the dissolution of the tablet might be the rate- limiting step in determining the onset of drug action.
- ❖ Compression can change the physical properties, particle size and crystal form of the drug can affect the proper action after administration.
- ❖ Sometimes the physical and chemical properties of the drug make it difficult to overcome compression problems such as capping, lamination, picking and sticking.

1.2. ADDITIVES USED IN TABLETS[2]

Ingredients in a tablet other than the active ingredient are called excipients. Excipients can help powders become more fluid. This fluid motion is very important for transferring powders into the die cavity for compaction. Excipients are used not only to enhance the performance of active ingredients, but also to simply make the active ingredients work better on the tablet press.

In the pharmaceutical industry it is a catch all term which includes such groups comprising diluents or fillers, binder or adhesives, disintegrants, lubricants, glidants or flow promoters, colors, flavours, fragrances, and sweeteners. All of these must meet certain criteria as follows.

- They must be physiologically inert.
- They must be physically and chemically stable.

- They must be free of any bacteria considered to be pathogenic or otherwise objectionable.
- They must not interfere with the bioavailability of the drug.
- They should be commercially available in form and purity commensurate to pharmaceutical standards.
- For drug products that are classified as food, such as vitamins, other dietary aids, and so on, the excipients must be approved as food additives.
- Cost must be relatively inexpensive.
- They must conform to all current regulatory requirements.

Diluents:

Diluents are fillers designed to make up the required bulk of the tablet when the drug dosage itself is inadequate to produce this bulk. Since combinations are also a possibility, consideration should be given to possible mixture.

Eg: Lactose, calcium carbonate, calcium phosphate, calcium sulphate, calcium dihydrate, Dibasic calcium phosphate, starch, dextrose, mannitol.

Disintegrants:

Disintegrants is the term applied to various agents added to the tablet granulation for the purpose of causing the compressed tablet to break apart (disintegrate) when placed in an aqueous environment. Disintegrants constitute a group of materials that, on contact with water, swell, hydrate, change in volume or form, or react chemically to produce disruptive changes in the tablet.

Eg. Micro crystalline cellulose, Starch, Croscarmellose sodium, Sodium starch glycolate, Methyl cellulose, Sodium carboxy methyl cellulose.

Binders:

Binders are the "glue" that hold powders together to form granules. They are adhesives that are added to the tablet formulations to provide the cohesiveness required for the bonding together of the granules under compaction to form the tablet. Binders are added either dry or in liquid form during wet granulation to form granules or to promote cohesive compacts for directly compressed tablets.

Eg. Starch, Povidone, Acacia, Gelatin, Tragacanth.

Lubricants:

Lubricants are used in the tablet formulations to ease the ejection of the tablet from the die, to prevent sticking of tablets to the punches, and to prevent excessive wear on punches and dies. Lubricants should be carefully selected for efficiency and for the properties of the tablet formulation.

Eg: Stearic acid, talc, silica and boric acid.

Anti adherents:

Anti adherents have the purpose of reducing sticking or adhesion of any of the tablet granulation or powder to the faces of the punches or to the die wall.

Eg: Magnesium stearate, talc and starch.

Glidants:

Glidants are materials that improve the flow characteristics of granulations by reducing interparticulate friction. They increase the flow of materials from larger to smaller apertures, from the hopper into the die cavities of the tablet press.

Eg: Talc, starch and silica.

Absorbents:

Absorbents are substances that are capable of holding quantities of fluid in an apparently dry state. Oil soluble drugs, fluid extracts or oil can be mixed with absorbent and then granulated and compressed into the tablets.

Eg: Fumed silica, microcrystalline cellulose, magnesium carbonate.

Coloring agents:

Coloring agents are incorporated into tablet generally for one or more of three purposes. First, colors may be used for product identification, production of a more elegant product and the continual decertification of many synthetic dyes. All colorants used in pharmaceutical must be approved and certified by the FDA. Two forms of color have typically been used in tablet preparation. These are the FD&C and D&C dyes.

Eg: Erythrosine, carmine and Quinoline yellow lake.

Flavouring agents:

Flavouring agents are incorporated into the formulation to give the tablet a more pleasant flavour or mask an unpleasant one. Aqueous (water soluble) flavours have found little acceptance due to their lesser stability upon aging.

Eg: Chocolate, peppermint and vanilla.

Sweetning agents:

Sweeteners are added primarily to chewable tablets when the commonly used carriers such as mannitol, lactose, sucrose, and dextrose do not sufficiently mask the taste of the components.

Eg: Saccharin, sucrose and aspartame.

1.3 TYPES OF TABLETS[3]

1.3.1 BASED ON ROUTE OF ADMINISTRATION:

I. Oral tablets for ingestion.

II. Tablets used in the oral cavity

III. Tablets administered by other routes.

IV. Tablets used to prepare solutions

I. ORAL TABLETS FOR INGESTION:

- Compressed tablets, multiple compressed tablets
- Layered tablets, compression coated tablets
- Repeat action tablets
- Delayed action and enteric coated tablets
- Sugar and chocolate coated tablets
- Film coated tablets
- Chewable tablets

II. TABLETS USED IN THE ORAL CAVITY:

- Buccal tablets
- Sublingual tablets
- Troches and lozenges Dental cones

III. TABLETS ADMINISTERED BY OTHER ROUTES:

- Implantation tablets
- Vaginal tablets

IV. TABLETS USED TO PREPARE SOLUTION

- Effervescent tablets
- Dispensing tablets
- Hypodermic tablets
- Tablet triturates

I. TABLETS INGESTED ORALLY

Orally ingested tablets are designed to be swallowed intact, with the exception of chewable tablets.

A) COMPRESSED TABLETS OR STANDARD COMPRESSED TABLETS:

Compressed tablets are prepared by a single compression, occur in various shapes and sizes and usually contain in addition to the medicinal substances, a number of pharmaceutical adjuncts including Binders, which help powders fuse or link particles to one another. Fillers, which bulk up a tablet. Lubricants, which prevent powders from sticking to the metal components of the tablet press and tablet – press tooling. Disintegrants that break up the tablet after being ingested. Several other excipients can be added to a formula to improve flow, compression, hardness, taste and tablet performance.

B) MULTIPLE COMPRESSED TABLETS:

Multiple compressed tablets are prepared by subjecting the fill material to more than a single compression. There are two classes of multiple compressed tablets.

- Layered tablets
- Compression-coated tablets

Both types may be either two-component or three component systems: two-or three – layer tablets, a tablet within a tablet, or a tablet within a tablet, within a tablet.

Both types of tablets usually undergo a light compression as each component is laid down, with the main compression being the final one. Tablets in this category are usually prepared

for one of the two reasons: to separate physically or chemically incompatible ingredients or to produce repeat-action or prolonged action products. In preparation of tablets within tablets, special machines are required to place the preformed core tablet precisely within the die for application of surrounding fill material.

C) REPEAT-ACTION TABLETS:

In Repeat-Action Tablets the core tablet is usually coated with shellac or an enteric polymer so that it will not release its drug load in the stomach. The second dose of drug is then added in the sugar coating, either in solution in the syrup or as a part of the dusting powder added for rapid coat builds up.

D) DELAYED-ACTION AND ENTERIC COATED TABLETS:

The delayed-action tablet dosage form is intended to release a drug after some time delay, or after the tablet has passed through one part of the GI tract into another. The enteric coated tablet is the most common example of a delayed-action tablet product. Enteric coated tablets are tablets with a coating that resist dissolution or disruption in the stomach but not in the intestine, thereby allowing for tablet transit through the stomach in favour of tablet disintegration, drug dissolution and absorption from the intestines.

Enteric coatings are employed when the drug substance is destroyed by gastric acid or is particularly irritating to the gastric mucosa or when bypass of the stomach substantially enhances drug absorption.

E) SUGAR AND CHOCOLATE-COATED TABLETS

Compressed tablets may be coated with a colored or uncolored sugar layer. The coating is water soluble and quickly dissolves after swallowing. The sugar-coat protects the enclosed drug from the environment and provides a barrier to objectionable taste or odor. The sugar coat also enhances the appearance of the compressed tablet and permits imprinting of identifying manufacturer's information. Sugar coating may add 50% of the weight and bulk of the uncoated tablet. Chocolate coated tablets are nearly a thing of the past. They are too easily mistaken for candy by children.

F) FILM COATED TABLETS:

Film coated tablets are compressed tablets coated with a thin layer of polymer capable of forming a skin like film. The film is usually coloured and it is more durable, less bulky,

and less time consuming to apply than sugar coatings. The coating is designed to rupture and expose the core tablet at the desired location in the gastrointestinal tract. Film coating can protect the tablet from light, temperature and moisture, mask undesirable taste or odor, improve the appearance, provide tablet identity, facilitate swallowing and control or modify the release of the drug.

G) CHEWABLE TABLETS:

Chewable tablets are intended to be chewed in the mouth prior to swallowing and are not intended to be swallowed intact. The purpose of the chewable tablet is to provide a unit dosage form of medication which can be easily administered to infants and children or to the elderly, who may have difficulty swallowing a tablet intact. The chewable tablet offers two major advantages to the delivery of a solid antacid dosage form. First, the dose of most antacids is large, so that the typical antacid tablet would be large to swallow, second the activity of an antacid is related to particle size.

II) TABLETS USED IN THE ORAL CAVITY

A) BUCCAL AND SUBLINGUAL TABLETS:

These two classes of tablets are intended to held in the mouth. Buccal and sublingual tablets are flat oval tablets intended to be dissolved in the buccal pouch (buccal tablets) or beneath the tongue (sublingual tablets) for absorption through the oral mucosa. Buccal tablets are designed to erode, slowly whereas for sublingual use (such as nitro-glycerine) dissolve promptly and provide rapid drug effects. Buccal and sublingual tablets dissolve slowly typically over a 15-30 minutes period, to provide for a effective absorption.

B) TROCHES AND LOZENGES:

These are two other types of tablets used in the oral cavity. Troches are designed to deliver medications directly to the mucus membranes of the mouth by dissolving slowly when placed between the tongue and gums. Troches are defined as a small medicated lozenge to exert a local effect in the mouth or throat. Lozenges can also be placed under the tongue and allowed to dissolve for sublingual delivery. This allows the medication to enter the blood stream quickly and easily. Lozenges can be enhanced with natural sweeteners. These tablet forms are commonly used to treat sore throat or to control coughing in the common cold.

C) DENTAL CONES:

Dental cones are relatively minor tablet forms that are designed to be placed in the empty socket following a tooth extraction. Their usual purpose is to prevent the multiplication of bacteria in the socket following extraction by employing a slow releasing Antibacterial Compound or to reduce bleeding by containing an astringent or coagulant.

III) TABLETS ADMINISTERED BY OTHER ROUTES

A) IMPLANTATION TABLETS:

Implantation or depot tablets are designed for subcutaneous implantation in animals or man. Their purpose is to provide prolonged drug effects ranging from one month to a year. They are usually designed to provide a constant drug release rate as possible. These tablets are usually small, cylindric, or rosette shaped and is typically not more than 8mm in length.

B) VAGINAL TABLETS:

Vaginal tablets or inserts are designed to undergo slow dissolution and drug release in the vaginal cavity. The tablets are usually ovoid or pear shaped to facilitate retention in the vagina. This tablet form is used to release antibacterial agents, antiseptics or astringent to treat vaginal infections.

IV) TABLETS USED TO PREPARE SOLUTION

A) EFFERVESCENT TABLETS:

Effervescent tablets are designed to produce a solution rapidly with the simultaneous release of carbon dioxide. The tablets are typically prepared by compressing the active ingredients with mixtures of organic acids – such as citric acid or tartaric acid and sodium bicarbonate. When such tablets is dropped into a glass of water, a chemical reaction is initiated between the acid and the sodium bicarbonate to form the sodium salt of acid, and to produce carbon dioxide and water. These tablets generally contain medicinal substances that dissolve rapidly when added to water. The reaction is quite rapid and is usually completed within one minute or less. In addition to having the capability of producing clear solutions, such tablets produce a pleasantly flavored carbonated drink, which assists in masking the taste of certain drugs.

B) DISPENSING TABLETS:

Dispensing tablets are also called as compounding tablets because the pharmacist used them to compound prescriptions. The tablets contains large amount of highly potent drug substances, so that pharmacist could rapidly obtain premeasured amounts for compounding multiple dosage units. Materials such as mild silver proteinate, bichlorides of mercury, merbromin and quaternary ammonium compounds are used to prepare the dispensing tablets.

C) HYPODERMIC TABLETS:

Hypodermic tablets are composed of one or more drugs with other readily water soluble ingredients and are intended to be added to sterile water or water for injection. They were originally used by physicians in extemporaneous preparation of parenteral solutions.

D) TABLET TRITURATES:

Tablet triturates are small, usually cylindric, molded or compressed tablets. The drugs employed in such products were usually quite potent and were mixed with lactose possibly a binder, such as powder acacia, after which the mixture was moistened to produce a moldable, compactable mass. This mass was forced into holes of a mold board fabricated from wood or plastic, after which the tablet were ejected using pegboard, whose pegs matched the holes in the mold. The tablets were then allowed to dry. Alcohol was commonly used to make wet powder mass.

1.4. TABLET MANUFACTURING PROCESS:[4]

A tablet with good characteristics is not made on a tablet press; it is made in the granulation process. Joined particles within a given granulation process will improve flow and compression characteristics, reduce segregation, improve content uniformity, and eliminate excessive amounts of fine particles. The results will be improved yields, reduced tablet defects, increased productivity and reduced down time. The objective of the process is to combine ingredients to produce a quality tablet.

GRANULATION

Granulation is the processes of collecting particles together by creating bonds between them. Bonds are formed by compression or by using a binding agent. The granulation process

combines one or more powders and forms a granule that will allow tableting process to be predictable and will produce quality tablets within the required tablet-press speed range.

A tablet formulation contains several ingredients apart from the active ingredient. The remaining ingredients are necessary because a suitable tablet cannot be composed of active ingredient alone. The tablet may require variations such as additional bulk, improved flow, better compressibility, flavoring, improved disintegration characteristics or enhanced appearance.

If the active ingredients in a formulation represent a very small portion of the overall tablet, then the challenge is to ensure that each tablet has the same amount of active ingredients. Sometimes, blending the ingredients is not enough. The active ingredients may segregate from the other ingredients in the blending process. The ingredients may be incompatible because of particle size, particle density, flow characteristics, compressibility and moisture content. These incompatibilities can cause problems such as segregation during blending or during transfer of the product to the press as well as separation of the active ingredients on the tablet press.

Granulating the active ingredient by itself and then blending it with the rest of the ingredients is one solution to the segregation problem or most of the ingredients could be granulated together. The best course of action to ensure that each tablet contains the correct amount of active ingredient, especially if the active is only a small percentage of the tablet ingredients, is to mix the active ingredients thoroughly with some or most of the other ingredients and then granulate the blend (i.e., from the blend into granules). Each granule would contain a little of each of the ingredients, and the active ingredient would be distributed evenly throughout the blend.

Three basic techniques are used to prepare powders for compression into a tablet

- Direct compression.
- Wet granulation
- Dry granulation.

WET GRANULATION:[5]

When powders are very fine, fluffy, will not stay blended, or will not compress, then they must be granulated. Wet granulation, the process of adding a liquid solution to powders, is one of the common ways to granulate. The process can be very simple or complex depending on the characteristics of the powders, the final objective of tablet making, and the availability of equipment.

Method:

Weighing and blending the ingredients: specified quantities of active ingredients, diluents or filler, and disintegrating agent are mixed by mechanical powder blend until uniform. A liquid binder is added to the powder mixture to facilitate adhesion of the powder until a damp mass resembling dough is formed. The wet mass is passed through a screen to prepare the granules. This may be done by hand or with special equipment. Granules may be dried in thermostatically controlled ovens that constantly record the time, temperature and humidity. After drying the granules are passed through a screen of a smaller mesh than that used to prepare the original granulation. Sizing of the granules are necessary so that the die cavities for tablet compression may be completely and rapidly filled by the free flowing granulation and fines should be added with this granules because void or air spaces left by too large a granulation result in production of uneven tablets. After dry screening, a dry lubricant is dusted over the spread out granulation through a fine mesh screen. After this process the granules were compressed into tablets.

DRY GRANULATION:[6]

The dry granulation process is used to form granules without using a liquid solution because the product to be granulated may be sensitive to moisture and heat. Forming granules without moisture requires compacting and densifying the powders. When a tablet press is used for tablet granulation, the powders may not possess enough natural flow to feed the product uniformly into the die cavity, resulting in varying degrees of densification. After weighing and mixing the ingredients, the powder mixture is slugged, or compressed into large flat tablets or pellets about 1 inch in diameter. The slugs are broken up by hand or by mill and passed through a screen and tablets are prepared by compression.

The roller compactor uses an auger-feed system that will consistently deliver powder uniformly between two pressure rollers. The powders are compacted into a ribbon or small pellets between these rollers and milled through a low – shear mill. When the product is compacted properly, then it can be passed through a mill and final being the compression into tablets. Roller compaction or dry granulation equipment offers a wide range of pressures and roll types to attain proper densification.

DIRECT COMPRESSION:[7]

Crystalline substances, such as sodium chloride, sodium bromide and potassium chloride may be compressed directly without the need of granulation since the above chemicals have free flowing and cohesive properties. For chemicals lacking this quality, special pharmaceutical excipients may be used to impart the necessary qualities for production of tablet by direct compression. As heat and water are not involved in direct compression method product stability can be improved. The capping, splitting, or lamination of tablets is sometimes related to air entrapment during direct compression. Forced or induced feeders can reduce air entrapment, making the fill powder more dense and suitable for compaction.

1.5 COATING:[8]

Coating is a process by which an essentially dry, outer layer of coating material is applied to the surface of a dosage form in order to confer specific benefits that broadly range from facilitating product identification to modifying drug release from the dosage form. The application of coating to tablets, which is an additional step in the manufacturing process, increases the cost of the product; therefore, the decision to coat a tablet is usually based on one or more of the following objectives.

- To mask the taste, odor or color of the drug.
- To provide physical and chemical protection for the drug.
- To control the release of the drug from the tablet.
- To protect the drug from the gastric environment of the stomach with an acid resistant enteric coating.

- To improve the pharmaceutical elegance by use of special colors & contrasting printing.

The general methods involved in coating of tablets are as follows:

I. FILM COATING:

Film coating is applied as a thin polymeric film to the surface of a tablet. Film coating can protect the tablet from light, temperature and moisture, mask undesirable taste or odor, improve the appearance, provide tablet identity, facilitate swallowing and control or modify the release of the drug.[20] Film coating solutions may be aqueous or non- aqueous.

FILM FORMER:[9]

A film former should be capable of producing smooth, thin films reproducible under conventional coating condition and applicable to a variety of tablet shapes. It should maintain the film strength and minimizes film cracking during handling or subsequent storage.

Film coating formulations usually contain the following components

1.Polymer
2.Plasticizer
3.Colorants/Opacifiers
4.Solvent/Vehicle
5.Flavoursandsweeteners
6.Surfactants
7.Antioxidants
8. Antimicrobials/Preservatives

They are explained below,

1) POLYMERS

A film former capable of producing smooth thin films reproducible under the prescribed coating conditions. Amongst the vast majority of the polymers used in film coating are cellulose derivatives or acrylic polymers and copolymers.

A) Immediate Release Coating Polymers

a) Cellulose derivates:

The most widely used of cellulosic polymers is HPMC (Hydroxypropyl Methyl Cellulose). It is readily soluble in aqueous media, forms film with good mechanical properties (strength, flexibility and adhesion to the tablet core).

Other examples: MC (Methyl Cellulose) & HPC (Hydroxypropyl Cellulose),

- **Hydroxyl Propyl Methyl Cellulose:** The polymer is prepared by reacting alkali treated cellulose first with methyl chloride to introduce methoxy groups and then with propylene oxide to introduce propylene glycol ether group. Hydroxy Propyl methyl cellulose closely approaches the desired attributes of an ideal polymer for film coating.

- **Methyl Hydroxy Ethyl Cellulose:** This polymer is prepared by reacting alkali treated cellulose first with methyl chloride and then with ethylene oxide. A wide variety of viscosity grades are available. It is structurally similar to Hydroxyl Propyl Methyl Cellulose. It is soluble in fewer organic solvents.

- **Ethylcellulose:** Ethylcellulose is manufactured by the reaction of ethyl chloride or ethyl sulfate with cellulose dissolved in sodium hydroxide. This material is completely in soluble in water & gastrointestinal fluids, and thus cannot be used alone for tablet coating. It is usually combined with other water soluble polymers to prepare films with reduced water soluble properties.

- **Hydroxypropyl cellulose:** Hydroxypropyl cellulose is manufactured by treatment of cellulose with sodium hydroxide, followed by a reaction with propylene oxide at an elevated temperature and pressure. It is soluble in water below 40° C, gastrointestinal fluids and many polar organic solvents.

- **Sodium Carboxy Methyl Cellulose:** Sodium Carboxy Methyl Cellulose is sodium salt of carboxy methyl cellulose and is manufactured by the reaction of soda cellulose with the sodium salt of monochloro acetic acid. It is available in low, medium, high and extra high viscosity grades. It is easily dispersed in water to form colloidal solution but insoluble in most organic solvents.

b). Vinyl derivatives

The most widely used vinyl polymer derivate is PVP. It has a limited use in film coating because of its inherent tackiness. A copolymer of PVP and vinyl acetate forms better films.

Povidone: Povidone is a synthetic polymer consisting of linear 1-vinyl-2-pyrolidinone groups. Povidone is available in various grades. The most common uses of povidone in pharmaceuticals is as a tablet binder and tablet coating material.

c). Polyethylene glycols:

Polyethylene glycols are manufactured by the reaction of ethylene glycol with ethylene oxide in the presence of sodium hydroxide at elevated temperature and under pressure. The materials with low molecular weights(200-600) are liquids at room temperature and are used as plasticizer for coating solution films.

d). Acrylate polymer:

Acrylate polymers are available only as organic solution and solid materials. These polymers produce films for the delayed action preparation similar to ethyl cellulose formulation.

B) Modified Release Coating Polymers

a) Extended release coating polymers

They are dissolved in organic solvent or dispersed in aqueous medium. Cellulose derivates also often used. Cellulose derivates are highly substituted cellulosic ether, thus rendering the polymer water-insoluble.

Example: Ethylcellulose.

b) Enteric Coating Polymers

An enteric coat is designed to resist the low pH of gastric fluids but to disrupt or dissolve when the tablet enters the higher pH of the duodenum. The important reasons for enteric coating are as follows;

- To protect acid-labile drugs form the gastric fluid.
- To prevent gastric distress or nausea due to irritation from a drug.
- To deliver drugs intended for local action in the intestines.
- To deliver drugs that are optimally absorbed in the small intestines to their primary absorption site in their most concentrated form.
- To provide a delayed- release component for repeat action tablet.

i) Phthalate derivative:

- **Cellulose acetate phthalate (CAP):** It has been widely used in the industry. It is also hygroscopic and relatively permeable to moisture and gastric fluids in comparison with some other enteric polymers. It dissolves only above pH 6. CAP films are brittle and usually formulated with hydrophobic film forming materials or adjuvants to achieve a better enteric film.
- **Hydroxypropyl methylcellulose phthalate:** They are derived from hydroxy propyl methylcellulose by esterification with phthalic anhydride. These polymers dissolve at a low pH (at 5 to 5.5) than CAP or acrylic co polymers, and this solubility characteristic may result in higher bioavailability of some specific drugs.
- **Polyvinyl acetate phthalate :(PVAP)** Polyvinyl acetate phthalate is manufactured by the esterification of a partially hydrolyzed polyvinyl acetate with phthalic anhydride. This polymer is similar to Hydroxypropyl methylcellulose phthalate in stability and pH dependent solubility.

ii) Acrylate derivative:

- **Acrylate polymers:** Two forms of commercially available enteric acrylic resins are Eudragit L and Eudragit S. Both resins produce films that are resistant to gastric fluid and are soluble in the intestinal fluids at pH at 6 and 7 respectively.

2) SURFACTANTS

Surfactants because of their chemical structure have tendency to accumulate at the boundary between two phases. They lower the interfacial tension between oil and water phases and also enhance the spreadability of the film during application. Eg: spans, tweens.

3) PLASTICIZERS

Affords flexibility and elasticity to the coat and thus provide durability. Plasticizers are simply relatively low molecular weight materials which have the capacity to alter the physical properties of the polymer to render it more useful in performing its function as a film coating material. It is generally considered to be mechanism of plasticizer molecules to interpose themselves between individual polymer strands thus breaking down polymer-polymer interactions. Thus polymer is converted in to more pliable materials.

Plastisizers are classifying in three groups. Polyos types contain glycerol, propylene glycol, PEG (Polyethylene glycol). Organic esters contain phthalate esters, dibutyl sebacete, citrate esters, triacetin. Oils/glycerides contain castor oil, acetylated, monoglycerides, fractionated coconut oil.

4) SOLVENTS/VEHICLES

The key function of a solvent system is to dissolve or disperse the polymers and other additives. Volatile organic solvents may be used to allow good spreadability of the coat components over the tablet and allowing rapid evaporation, but they are expensive and show environmental hazards and solvent residue in the formulation must be investigated (certain limit). Aqueous vehicles are safer, but they show slower evaporation and may affect drug stability.All major manufactures of polymers for coating give basic physicochemical data on their polymers. These data are usually helpful to a formulator.

The major classes of solvents being used are,

a. Water

b.Chlorinatedhydrocarbons

5) COLORANTS/OPACQUANTS

Provides an elegant appearance. Ex.: Iron, oxide, pigment, Titanium dioxide and Aluminum lakes. Identification of the product by the manufacturer and therefore act as an aid for existing GMP procedures.

- ✓ Reinforcement of brand imaging and reduction in product counterfeiting.
- ✓ Identification of the product by patients by using colourants.

Colorants for film coating are having, in more or less amount, property of opacifier. So they would give protection to active ingredients in presence of light. Colorants are mainly classified in to three parts. Sunset yellow, tartrazine, erythrosine are examples of Organic dyes and their lakes. Iron oxide yellow, red and black, titanium dioxide, talc are the examples of Inorganic colours. Anthrocyanins, ribofloavine and carmine are the examples of natural colours.

6) FLAVORS AND SWEETENERS are added to mask unpleasant odours or to develop the desired taste. For example, aspartame, various fruit spirits (organic solvent), water soluble pineapple flavour (aqueous solvent) etc.

7) ANTIOXIDANTS are incorporated to stabilize a dye system to oxidation and colour change. For example oximes, phenols etc.

8) ANTIMICROBIALS/PRESERVATIVES are added to put off microbial growth in the coating composition. Some aqueous cellulosic coating solutions are mainly prone to microbial growth, and long-lasting storage of the coating composition should be avoided. For example alkylisothiazloinone, carbamates, benzothiazoles etc.

II. SUGAR COATING:

Sugar coating serves the various purposes of protecting the drug from the air and humidity and providing a taste or a smell barrier to objectional tasting and smelling drug. Sugar coating is a multistep process. Tablets intended to be coated are manufactured to be thin edged and highly convex to allow the coatings to form rounded rather than angular edges. The sugar coating of tablets may be divided into the following steps:

1) **SEAL COATING:** Seal coat is necessary to protect the tablet core from the aqueous nature of sucrose application. Sealing also prevents certain types of materials from migrating to the surface tablets and spoiling the appearance. Shellac is used as water impervious polymer. Shellac is insoluble in water but shows solubility in aqueous alkalis, it is moderately soluble in warm ethanol. The application of sealant is followed by an application of dusting powder to prevent tackiness.

2) **SUB COATING:** During the sugar coating process the increase in the weight achieved can be 30 – 50% of the weight of the original tablet core. Much of the added weight is applied at the sub coating stage. Sub coating serves the confer on the tablet core a perfectly rounded aspect. A sub coating suspension containing both the binder and the insoluble powder is sprayed intermittently on the tablet bed. The product at the end of the sub coating will be too rough to continue with color coating.

3) **SMOOTHING AND FINAL ROUNDING: A**fter the tablets are sub coated, 5 to 10 additional coatings of thick syrup are applied to complete the rounding and smooth the coatings. This syrup is sucrose based, with or without additional components such as starch and calcium carbonate.

4) **FINISHING AND COLORING:** To attain final smoothness and the appropriate color to the tablets, several coats of thin syrup containing the desired colorants are applied in the usual manner. This step is performed in a clean pan, free from previous coating materials.

5) **POLISHING:** After the coloring process the tablet have a somewhat dull appearance which requires a separate polishing step to give them the high degree of gloss traditionally associated with sugar coated tablets. Application of an organic solvent/ suspension of waxes e.g beeswax or carnauba is generally used.

1.5. QUALITY CONTROL PARAMETERS:[10]

1.5.1. GRANULES CHARACTERISTICS:

- **Flowability:**

Press speed requires powders to be very fluid, a property commonly referred to as product flow ability. Good flow characteristics are necessary because the mechanical action

of the tablet press requires a volume of fill. A tablet press does not weigh the precise amount of powder for each tablet. To achieve consistent tablet weights, the tablet press must be designed to flow consistently and to fill volumetrically. Thus the granules (or powders, for direct compression) must possess a consistent particle- size distribution and density to attain proper flow and achieve volume of fill. In other words, the powders must flow consistently to attain consistent results.

- **Compressibility:**[11]

A powder with a high compressibility forms tablets with a high resistance towards fracturing and without tendencies to cap or laminate. In practice, the most common way to assess powder compressibility is to study the effect of compression pressure on the strength of the resulting tablet. Compressing a tablet of many different powders that have varying physical characteristics can be difficult. If the formula has some of both characteristics -large particles with high moisture content and small, dry particles- then the tablet may or may not compress well and probably will have difficulty holding together. One of the main reasons to granulate powders is to make them more compressible.

- **Bulk density and tapped density:**

Bulk density is determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder or through a volume measuring apparatus into a cup. The bulk density often is the bulk density of the powder as poured or as passively filled into a measuring vessel. Because the interparticulate interactions that influence the bulking properties of a powder are also the interactions that interfere with powder flow, a comparison of the bulk and tapped densities can give a measure of the relative importance of these interactions in a given powder. Such a comparison is often used as an index of the ability of the powder to flow.

- **Tapped density:**

It is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume the cylinder is mechanically tapped, and volume readings are taken until further volume has not changed. Mechanical tapping is achieved by raising the cylinder and allowing it to drop under its own weight.

1.5.2. COMPRESSED TABLET CHARACTERISTICS:[12]

- **General appearance:**

The general appearance of the tablet, its visual identity and overall "elegance" is essential for consumer acceptance, for control of uniformity in tablet lot and for monitoring trouble free manufacturing. It involves monitoring different attributes like tablet's shape, size, color, presence or absence of odor, taste, surface texture, physical flaws, consistency, and legibility of any identifying markings.

- **Tablet thickness:**

The thickness of a tablet is determined by the diameter of the die, the amount of fill permitted to enter the die, the compaction characteristics of the fill material, and the force or pressure applied during compression. Tablet thickness is measured with a caliper or thickness gauge which measures the thickness in millimeters.

- **Tablet hardness:**

The resistance of the tablet to chipping, abrasion or breaking under conditions of storage, transportation and handling before usage depends on its hardness. A hardness tester measures the force required to break the tablet when the force generated by a spring is applied diametrically to the tablet. Hardness (crushing strength) determinations are made throughout the tablet runs to determine the need for pressure adjustments on the tableting machine. If the tablet is too hard, it may not disintegrate in the required time period or meet the dissolution specification.

- **Tablet friability:**

The term friability is the ability of the tablet to withstand abrasion in packaging, handling and shipping. In a friablator, a number of tablets are weighed and placed in the tumbling apparatus where they are exposed to rolling and repeated shocks resulting from freefalls within the apparatus. After a given number of rotations the tablets are weighed and the loss in weight indicates the ability of the tablets to withstand this type of wear.

❖ **Weight variation:**

The volumetric fill of the die cavity determines the weight of the compressed tablet. In setting up the tablet machine the fill is adjusted to give the desired tablet weight. The weight of the tablet is the quantity of the granulation which contains the labeled amount of the therapeutic ingredient. The weight of the tablet being compressed is checked routinely so as to assure that tablet contains desired amount of the drug. For the tablets that contain more than 90% of the drug then weight variation test can be used as drug content uniformity of the tablet. Specified number of tablets is taken at random manner and average weight was determined. The average weight of tablets should not deviate from the maximum percentage deviation allowed.

❖ **Content uniformity:**

It is the intended amount of drug substance contained by every tablet with little variation among tablets within a batch. A fundamental quality attribute for all pharmaceutical preparation is the requirement for a constant dose of drug between individual tablets. Specified numbers of tablets are individually assayed for their content and requirements for content uniformity are met if the amount of active ingredient in each dosage unit lies within the range specified in the monograph.

❖ **Disintegration:**

The disintegration test is a measure only of the time required under a given set of conditions for a group of tablets to disintegrate into particles. This test is useful as a quality – assurance tool for conventional (non sustained- release) dosage forms. Specified number of tablets was placed in the disintegration apparatus and the process is continued until the tablets get disintegrated.

❖ **Dissolution:**

Since drug absorption and physiological availability depend on having the drug substance in the dissolved state, suitable dissolution characteristics is important property of a satisfactory tablet. The dissolution test for measuring the amount of time require for a given percentage of the drug substance in the tablet to go into the solution under a specified set of condition is an *in-vitro* test. Specified numbers of tablets were taken in a dissolution apparatus containing suitable medium and the test is performed as per the specifications.

2. AIM AND OBJECTIVE

The aim of the present study is to formulate and evaluate Film coated tablets of Fexofenadine Hydrochloride for the effective treatment of "Seasonal allergic rhinitis" and for treatment of "Chronic urticaria".

The main objective of this study was:

- To perform the preformulation studies.
- To formulate Fexofenadine Hydrochloride immediate release tablets.
- To select the best formulation based on in-vitro studies for film coating.
- To perform stability studies on the most satisfactory formulation.
- To correlate with innovator product.

3. PLAN OF WORK

The present work was carried out to formulate film coated Fexofenadine Hydrochloride tablets and to evaluate the *in-vitro* dissolution and stability studies for the prepared film coated Fexofenadine Hydrochloride tablets. It was planned to carry out this work as outlined below.

- Literature review.
- Drug profile.
- Excipients profile.
- Evaluation of API.
- To perform drug and excipients compatibility studies.
- Evaluation for the pre-compression parameters.
- To formulate uncoated Fexofenadine Hydrochloride tablet by wet granulation method.
- To evaluate the formulated uncoated Fexofenadine Hydrochloride tablets for the

  Following parameters.

  a) Tablet thickness.
  b) Weight variation.
  c) Tablet friability.
  d) Content uniformity.
  e) Tablet hardness.
  f) Disintegration.
  g) Dissolution

- To coat the compressed tablet by film coating process using Hydroxypropyl Methylcellulose (film polymer). Pan coating method was going to be used.
- To evaluate the prepared film coated Fexofenadine Hydrochloride tablets.
- To carry out the comparative *in-vitro dissolution* studies of prepared film coated Fexofenadine Hydrochloride tablet with the innovator product.
- Stability studies on selected batch.

4. REVIEW OF LITERATURE

- **Nagendra Kumar D et al.,**[13] formulated fast dissolving tablets of fexofenadine hydrochloride to enhance patient compliance by sublimation method. In this method, camphor was used as the subliming agent (upto 30% w/w), crospovidone and croscarmellose sodium (2-8% w/w) as super disintegrants. The formulation, containing 8% w/w of crospovidone and 30% w/w camphor as the subliming agent emerged as the overall best formulation (t50%4.3 min) based on drug release characteristics in pH 6.8 phosphate buffer compared to commercial conventional tablet formulation (t50%15 min).

- **Farya Zafar et al.,** [14] formulated and evaluated Fexofenadine 120mg tablets using low – cost directly compressible excipients. Three different formulations (F1-F3) were prepared by direct compression method using Avicel pH 101 in the range of 35-38%, Magnesium Stearate was used in the ratio of 2-3% and Crospovidone was used from 7-9% in F1-F3. Among three formulations, F3 showed comparatively better results against different parameters as compared to F1 and F2. F3 showed 103.12% drug release, required 13 sec for disintegration and 100.18% assay and weight variation of 224.77+1.49. Results indicated that direct compression is capable to manufacture tablets with excellent physical properties and showed adequate disintegration and dissolution.

- **Ana R et al.,**[15] developed and validated the dissolution tests for Fexofenadine hydrochloride capsules and coated tablets using an HPLC method. The appropriate conditions were determined after testing sink conditions, dissolution medium, and agitation intensity. The apparatus, paddle and basket, were applied to tablets and capsules, respectively. Fexofenadine hydrochloride capsules, products A and B, and coated tablets, products A, B and C were evaluated. The best dissolution conditions tested, for the products in each respective pharmaceutical dosage form were applied to evaluate the dissolution profiles. The parameters of difference factor, similar factor, and dissolution efficacy were employed.

- **Shah arpitkumar p. et al.,**[16] formulated tasteless complexes of Fexofenadine Hydrochloride with Kyron-134 and to formulate tasteless complex into fast-Dispersible

tablets (FDT).Tasteless Drug resin complexes (DRC) were prepared using combination of Kyron-134 & drug in different ratio (1:3) and evaluated for different factor affecting Drug-Resin Complexation, Complexation time, stirring time, soaking time, temperature, and effect of pH on Fexofenadine Hydrochloride loading on Kyron-134. Fexofenadine Hydrochloride release from FDT is obtained at salivary and gastric pH. Drug release from FDT in salivary pH was insufficient to impart bitter taste. Complete drug release was observed at gastric pH.

- **Hongxia Lin et al.,**[17] the effect of various surfactants (sodium cholate, sodium taurocholate, Tween 80 and Poloxamer F68) on enhancing the transepithelial permeabilityof Fexofenadine HCl was evaluated in a human nasal epithelial cell monolayer model. A dose-dependent reduction of cell viability was observed at higher than critical micelle concentration (CMC) of the surfactants, and the IC50 of non-ionic surfactants (Tween 80 and Poloxamer F68) was higher than that of ionic surfactants (sodium cholate and sodium taurocholate). These results imply that ionic surfactants are potentially useful permeation enhancers for nasal delivery of hydrophilic compounds, such as Fexofenadine HCl.

- **kuldeep yogendra desale, P D et al.,**[18] fast dissolving tablets of fexofenadine HCl were designed with a view to enhance patient compliance by direct compression method. The present work studied the effect of superdisintegrants on release rate of fexofenadine HCl in the form of fast disintegrating tablet. The superdisintegrants used were crosscarmellose sodium, crosspovidone and kyron T-314. The blends were prepared by direct compression technique. The tablets were evaluated for hardness, thickness, friability, drug content, weight variation and *in-vitro* drug release studies in pH 6.8.

- **Pradeep kumar T. at al.,**[19] developed the pharmaceutically equivalent, stable, cost effective and quality improved formulation of film coated Ticlopidine Hydrochloride tablets by direct compression technique. The three super disintegrant used in the study were croscarmellose sodium, microcrystalline cellulose and pregelatinised starch. The formulation containing combination of croscarmellose sodium, microcrystalline cellulose and Pregelatinised starch (6, 44.73, 54,75mg) showed minimum disintegration time and maximum drug release.

- **Nasiruddin Ahmad farooqui et al.,**[20] formulated film coated tablets of Secnidazole by wet granulation method and the granules were compressed for tablets and they were coated with polymer for getting film coated tablets at specified conditions and the evaluation of film coated tablets were evaluated for various parameters as description, average weight, weight variation, hardness test, thickness, dissolution, related substances disintegration time and assay of tablet for compliance with acceptance criteria for formulation of Secnidazole film coated tablets.

- **Damodrharan .N et al.,**[21] developed small intestine targeting tablets of Doxycycline Hydrochloride by wet granulation method and enteric coated tablets. Six batches (F1-F6) were formulated and evaluated for hardness, friability, weight variation, drug release, disintegration time and drug content. Among the six formulation F4 was showing 94% drug release and considered to be best formulation.

- **D. Srinivas, suhal Debnath et al.,** [22] formulated film coated tablet of Valsartan by direct compression, slugging and wet granulation techniques exhibited the good powder flow than direct compression technique. Based on this investigation results, the drug release from tablets increase with increasing concentration of super disintegrant.

- **R. Natarajan Paroxetine et al.,**[23] formulated various formulations of immediate release tablet of Paroxetine using different superdisintegrants (Sodium Starch Glycolate, Croscarmellose, Crospovidone) and different grades of dicalcium phosphate by wet granulation method. The in vitro dissolution studies show the release is in the following order of superdisintegrants: Sodium Starch Glycolate > Croscarmellose > Crospovidone. These results suggest that, as determined by f2 factor (similarity factor) and maximum in vitro dissolution was found to be with Formulation F-7 and it clearly shows due to Sodium Starch Glycolate (4%).

- **Y. Dastagiri Reddy et al.,**[24] formulated Gemfibrozil as Immediate release tablets using micro crystalline cellulose, pregelatinized starch, sodium starch glycollate and calcium stearate as excipient. It was compared with the innovator and effect of LOD on Gemfibrozil immediate release tablets were studied and to evaluated and the best formulations were coated with opadry white and comparative invitro dissolution profile of the coated formulation with that of the innovator product had shown that F6

formulation best matched with innovator and the formulations are loaded for the stability studies.

- **Jampani N et al.,**[25] Formulated immediate release tablets of Candesartan Cliexetil, prodrug of Candesartan by changing the concentration of ingredients. The immediate release tablets were prepared by wet granulation method to provide rapid onset of action. The main ingredients used in the formulations were lactose monohydrate, PEG, calcium CMC and MCC. The formulation containing 38% of MCC was selected as the optimized product because of the best results obtained from various test.

- **Galge Deepak et al.,**[26] Formulated immediate release tablets of Irbesartan by wet granulation method. Effect of various fillers and disintegrants were also explored. MCC, Colloidal silicone dioxide, croscarmellose sodium were used in the method. Final selection of the optimized batch was done based on pharmaceutical equivalence of development formulation to that of marketed one.

- **Shridhar J Pandya et al.,**[27] formulated Fexofenadine hydrochloride complex with inclusion complex with β-Cyclodextrin, because Fexofenadine hydrochloride having a poorly solubility and bioavailability. Inclusion complex with β-Cyclodextrin improve the characteristic and dissolution rate as compare to marketed product. Fexofenadine hydrochloride is an antihistaminic agent used for treatment of relieving hay fever and allergy symptoms, such as sneezing and red, itchy, tearing eyes. Its poor solubility is major problem for the patient compliance. Within 30 min, more than 90 % drug was released from the complexes, were good as compare to marketed product which shown in release profile.

- **Chowhan et al.,**[28] studied the comparative evaluations of aqueous film coated tablet formulations by high humidity aging. Compressed tablets of ticlopidine hydrochloride were coated with three aqueous film coating formulations and aged under 95% relative humidity at 23° and 37°. The *in vitro* dissolution of the drug from tablets coated with the formulation containing polymethacrylic acid esters before aging was slower than the tablets coated with the formulations containing hydroxypropyl methylcellulose or ethylcellulose dispersion. On aging, the *in vitro* drug dissolution of the coated and uncoated tablets decreased and the decrease depended on the film forming excipient in

the coating formulation and the temperature of aging. The tablets coated with the formulation containing polymethacrylic acid esters dissolved very slowly after aging.

- **Ruotsalainen et al.,**[29] studied aqueous film coating of tablets performed in a side – vented pan coater. The effects of film coating conditions and storage, surface morphology, moisture content and stability of hydroxyl propyl methyl cellulose coated tablets containing a moisture labile drug ASA were investigated. In addition, the time dependent dimensional changes of film coated tablets and the relevance of these changes to film adhesion were measured. The surface roughness was measured using a non contacting laser profilometer an optical roughness analyzer and a confocal laser scanning microscope. Process automation with an air flow rate measurement system, data storage and monitoring capability was used to control and analyse the film coating process.

- **Bytul M. Rahman et al.,**[30] prepared and evaluated the ketorolac tromethamine tablets with higher dissolution rates and compare them with marketed product. Direct compression method was adopted for preparation of tablet using different excipients namely; microcrystalline cellulose, spray dried lactose and starch 1500. The effect of excipients on the drug release from prepared tablets was also studied. All the tablet quality control tests were studied. All formulations showed good mechanical properties and complied with the USP 28 pharmacopeial standard requirements for uniformity of dosage units and friability. Formula No. 2 containing starch 1500 and microcrystalline cellulose gave higher percentage of ketorolac tromethamine release in comparison with other formulations and marketed product.

- **Tejash Serasiya*1 et.al**,[31] dispersible tablets of pheniramine maleate were prepared by direct compression method using various super disintegrants like Crospovidone, croscarmellose sodium, sodium starch glycolate, low substituted hydroxypropyl cellulose, pregelatinized starch. The tablets were disintegrating in–vitro within 20 to 51 sec. Dissolution studies revealed that formulations containing 10% Crospovidone and formulation containing 10% croscarmellose sodium showed 100% of drug release, at the end of six min. The concentration of super disintegrants had an effect on disintegration time and in-vitro drug dissolution whereas hardness and friability of resulting tablets were found to be independent of disintegrant concentration. The two

formulations, one containing 10% of Crospovidone and second containing 10% croscarmellose sodium were found to give the best results.

- **Abdel Naser Zaid et al.,**[32] to developed and evaluated the stability of film coated Atorvastatin Calcium (AtC) tablets using Opadry-OY-B-28920. AtC uncoated tablets were developed and manufactured through the Wet Granulation process. Opadry-OY-B-28920 white aqueous coating dispersion was used as film coating material. That aqueous film coating with Opadry-OY-B-28920 system is an easy and economical approach for preparing stable film coated AtC tablet of immediate release.

- **Heena Chaudhary et al.,**[33] formulated Fexofenadine hydrochloride is almost completely absorbed from the gastro-intestinal tract following oral administration, but bioavailability is reported to be only about 45% due to hepatic first-pass metabolise, to prepared Transdermal patch of Fexofenadine hydrochloride. Preparation of transdermal patches of Fexofenadine hydrochloride using polymers: Hydroxypropyl methyl cellulose, Ethyl cellulose plasticized with Glycerol. The patches were evaluated for various parameters like Thickness, Water-Vapor Permeability, Tensile Strength, Drug Content, Diffusion and Dissolution studies. Prepared patches exhibited Zero Order Kinetics and the permeation profile was matrix diffusion type. *In-vitro* release study of Fexofenadine hydrochloride transdermal patch shown release of drug 79 % at 24 h and also follows zero order kinetics release.

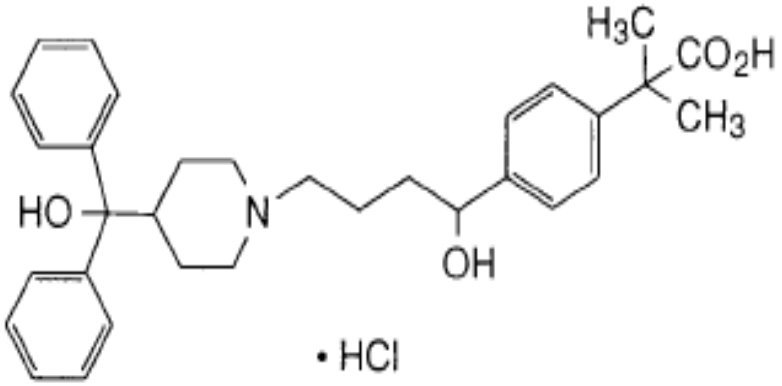
- **Piao HM et al.,**[34] to enhance the solubility and bioavailability of poorly absorbable Fexofenadine, micro emulsion system composed of oil, surfactant and co-surfactant was developed for intranasal delivery. An increase in the micro emulsion region in pseudo-ternary phase systems was observed with increased surfactant concentration. The optimized micro emulsion formulations showed higher solubulization of Fexofenadine, i.e., F1 (22.64 mg/ml) and F2 (22.98 mg/ml), compared to its intrinsic water solubility (1.51 mg/ml). tmax was observed within 5 min after intranasal administration at 1.0 mg/kg dose, and the absolute bioavailability (0-4 h) was about 68% compared to the intravenous administration in rats. Our results suggested that these micro emulsion formulations could be used as an effective intranasal dosage form for the rapid-onset delivery of Fexofenadine.

5. DRUG PROFILE [35]

FEXOFENADINE HYDROCHLORIDE

DRUG **:** Fexofenadine Hydrochloride.

Structural Formula:



Molecular Formul **:** $C_{32}H_{39}NO_4$.HCL.

Chemical Name **:** (±)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-iperidinyl]-butyl]-α, α- dimethyl benzene acetic acid hydrochloride.

Molecular Weight **:** 538.13

Category **:** Histamine H_1-receptor antagonist.

Dose **:** 30mg, 60mg, 180mg.

Description **:** Fexofenadine hydrochloride is a white to off-white crystalline powder.

Solubility **:** Freely soluble in methanol and ethanol, slightly soluble in chloroform and water, and insoluble in hexane.Melting Point Range: 142.6^0C

MECHANISM OF ACTION: [36]

Fexofenadine hydrochloride, the major active metabolite of Terfenadine, is an antihistamine with selective peripheral H1-receptor antagonist activity. Both enantiomers of Fexofenadine hydrochloride displayed approximately equipotent antihistaminic effects. Fexofenadine hydrochloride inhibited antigen-induced bronchospasm in sensitized guinea pigs and histamine release from peritoneal mast cells in rats. The clinical significance of these findings is unknown. In laboratory animals, no anti cholinergic or alpha1-adrenergic blocking effects were observed. Moreover, no sedative or other central nervous system effects were observed. Radiolabeled tissue distribution studies in rats indicated that Fexofenadine does not cross the blood-brain barrier.

PHARMACOKINETICS:

Absorption:

Fexofenadine hydrochloride is rapidly absorbed after oral administration with peak plasma concentrations being reached in 2 to 3 hours.

Distribution:

Fexofenadine hydrochloride is 60% to 70% bound to plasma proteins, primarily albumin and α1-acid glycoprotein.

Metabolism:

About 5% of the total dose is metabolized, mostly by the intestinal mucosa, with only 0.5 to 1.5% of the dose undergoing hepatic biotransformation.

Elimination:

Elimination half-life of about 14 hours has been reported although these may be prolonged in patients with renal impairment. Excretion is mainly in the faeces with only 10% being present in the urine. Fexofenadine hydrochloride dose not cross the blood brain barrier.

ADVERSE REACTIONS:[37]

The most common adverse reactions were headache, back pain, dizziness, stomach discomfort, drowsiness, fatigue, nausea, dyspepsia and dysmenorrhoea.

PRECAUTIONS:

Patients with decreased renal function should be given a lower initial dose (one tablet per day) because they have reduced elimination of Fexofenadine.

INDICATIONS:

Seasonal Allergic Rhinitis

Fexofenadine hydrochloride tablets are indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children's of 6 years age and older.

Chronic Idiopathic Urticaria

Fexofenadine hydrochloride tablets are indicated for treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children's of 6 years age and older.

CONTRAINDICATIONS:

Fexofenadine hydrochloride tablets are contraindicated in patients with known hypersensitivity to Fexofenadine and any of the ingredients of Fexofenadine hydrochloride. Rare cases of hypersensitivity reactions with manifestations such as Angioedema, chest tightness, dyspnea, fushing and systemic anaphylaxis have been reported.

DOSAGE AND ADMINISTRATION:[38]

Seasonal Allergic Rhinitis and Chronic Idiopathic Urticaria:

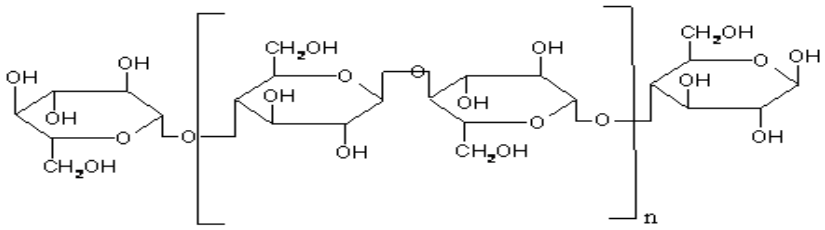
Adults and Children's of 12 Years and Older: The recommended dose of Fexofenadine hydrochloride tablets is 60 mg twice daily or 180 mg once daily. A dose of 60 mg once daily is recommended as the starting dose in patients with decreased renal function.

Children's of 6 to 11 Years: The recommended dose of Fexofenadine hydrochloride tablets is 30 mg twice daily. A dose of 30 mg once daily is recommended as the starting dose in pediatric patients with decreased renal function.

6. EXCIPIENTS PROFILE (6.1- 6.12)[40]

6.1. MICROCRYSTALLINE CELLULOSE

Structural formula



Non proprietary name

BP	:	Microcrystalline cellulose
JP	:	Microcrystalline cellulose
PhEur	:	Cellulosum microcrystallinum
USPNF	:	Microcrystalline cellulose

Empirical formula

$(C_6H_{10}O_5)$ n

Molecular weight

≈36000 where n≈220.

Synonym

Avicel, Cellulose gel, Tabulose Crystalline cellulose, E460, Emcocel, Fibrocel, Vivacel

Chemical name

Cellulose

Functional category

Adsorbent, suspending agent, tablet disintegrant, capsule and tablet diluents.

Physical state

It is purified, partially depolymerised Cellulose that occurs white, odourless, tasteless, crystalline powder composed of Porous particles.

Typical properties

Density (bulk) - 0.337 g/cm^3

Density (tapped) - 0.478 g/cm^3

Density (true) -1.512-1.668 g/cm^3

Melting point - Characteristics at 260-270^{o}C

Table No: 1 Properties of some commercially available grades of microcrystalline cellulose

Grade	Nominal mean particle size(µm)	Particle size analysis		Moisture content (%)
		Mesh size	Amount retained (%)	
Avicel PH-101	50	60 200	≤1.0 ≤30.0	≤5.0
Avicel PH-102	100	60 200	≤8.0 ≥45.0	≤5.0
Avicel PH-103	50	60 200	≤1.0 ≤30.0	≤3.0
Avicel PH-105	20	400	≤1.0	≤5.0
Avicel PH-112	100	60	≤8.0	≤1.5
Avicel PH-113	50	60 200	≤1.0 ≤30.0	≤1.5
Avicel PH-200	180	60 100	≥10.0 ≥50.0	≤5.0
Avicel PH-301	50	60 200	≤1.0 ≤30.0	≤5.0
Avicel PH-302	100	60 200	≤8.0 ≥45.0	≤5.0

Solubility

Slightly soluble in 5% w/v Sodium Hydroxide solution, Practically insoluble in water, acids, and most Organic solvents.

Stability & Storage condition

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well closed container in a cool and dry place.

Incompatibilities

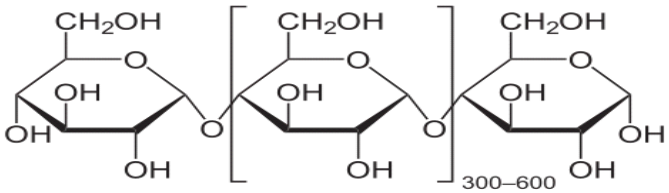
Incompatible with strong oxidizing agents.

Applications

It is widely used in pharmaceuticals, primarily as binder/ diluents in oral tablet and capsule formulations. Where it is used in both wet granulation and direct compression processes. MCC also has some lubricant and disintegrant properties that make it useful in tableting.

6.2. PREGELATINISED STARCH

Structural formula



Non proprietary name

USP : Pregelatinised starch.

PhEur : Starch, Pregelatinised.

Synonym

Compressible starch, instant starch, starch1500, prejel.

Chemical name

Pre-gelatinised starch.

Empirical formula

$(C_6H_{10}O_5)_n$

Molecular weight

300-100g/mol.

Functional category

Tablet and capsule binder, diluent, disintegrant.

Physical state

Moderately coarse to fine, white to off-white coloured powder. It is odorless and has a slight characteristic taste.

Typical properties

Density (Bulk) **:** 0.586 g/cm^3

Density (tapped) **:** 0.879 g/cm^3

Density (true) **:** 1.156 g/cm^3

Solubility

Slightly soluble in cold water.

Insoluble in organic solvents.

Stability & Storage condition

It is a stable though hygroscopic material, which should be stored in a well- closed container in a cool and dry place.

Applications

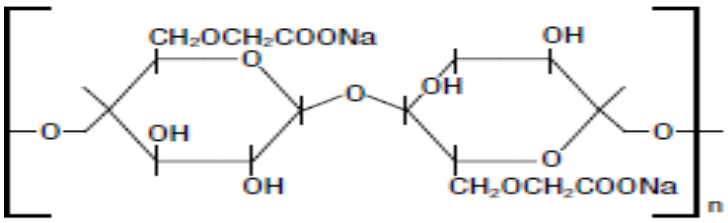
Pregelatinised starch is a modified starch used in tablet formulations as a binder, diluents, and disintegrant. It may be used as a binder in wet granulation and dry compression processes.

Table No: 2 Different concentration of Pregelatinised Starch

Use	Concentration (%)
Tablet binder (wet granulation)	5–75
Tablet disintegrant	5–20
Diluent (hard gelatin capsules)	5–10
Tablet binder (direct compression)	5–10

6.3 CROSCARMELLOSE SODIUM

Structural formula



Non proprietary name

BP : Croscarmellose sodium

JPE : Croscarmellose sodium

USP : Croscarmellose sodium

Molecular weight

90,000-7,00,000**.**

Synonym

Ac-Di-Sol, Solutab, Primellose, Pharmacel Xl

Chemical name

Cellulose, Carboxy methyl ether,

Physical state

Croscarmellose sodium occurs as an odourless, white coloured powder.

Functional category

Tablet and capsule disintegrant

Typical properties

Density (bulk)	:	0.529 g/cm^3
Density (tapped)	:	0.819 g/cm^3
Density (true)	:	1.543 g/cm^3

Solubility

Insoluble in water rapidly swells to 4-8 times of its original volume on contact with water.

Stability & Storage Condition

Croscarmellose sodium is a stable though hygroscopic material. It should be stored in a well-closed container in a cool, dry place.

Incompatibilities

The efficacy of Croscarmellose sodium may be slightly reduced in tablet formulations prepared by either wet granulation or direct compression process which contains hygroscopic excipients such as Sorbitol.

Applications

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for tablet, capsule and granules. In tablet formulations, croscarmellose sodium may be used in both direct compression and wet granulation processes.

Table No: 3 Different concentration of Croscarmellose sodium

Use	Concentration (%)
Disintegrant in capsules	10-25%
Disintegrant in tablets	0.5-5.0%

6.4. LACTOSE MONOHYDRATE

Nonproprietary Names

BP : Lactose monohydrate

USPNF : Lactose monohydrate

Chemical Name : O-β-D-Galactopyranosyl-(1-4)-α-D-glucopyranose monohydrate

Emprical Formula

$C_{12}H_{22}O_{11}.H_2o$

Molecular Weight

360.31

Functional category

Binding agent; diluents for dry-powder inhalers; tablet binder, tablet and capsule diluents

Physical state

Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; α- lactose is approximately 20 % as sweet as sucrose, while β-lactose is 40% as sweet.

Typical Properties

Angle of repose: 33^{o} for Pharmatose DCL 15; 32^{o} for Tablettose 70 and Tablettose 80

Density (true) **:** 1.545 g/cm^{3} (α-lactose monohydrate)

Melting point **:** 201-202^{o}C (for dehydrated α-lactose monohydrate)

Moisture content

Lactose monohydrate contains approximately 5% w/v water of Crystallization and normally has a range of 4.5-5.5% w/v water content.

Solubility

Table No: 4 Solubility of lactose monohydrate in different solvents

Solvent	**Solubility at 20^{o}c unless otherwise stated**
Chloroform	Practically insoluble
Ethanol	Practically insoluble
Ether	Practically insoluble

Stability & Storage conditions

Lactose should be store in a well closed container in a cool dry place.

Applications

Lactose is widely used in tablets and capsules as filler, and to a more limited extent in lyophilized products and infant formulas. It is used in dry-powder inhalation as diluents. Usually, in the preparation of tablets by wet-granulation method or milling, fine grades of lactose are used. Lactose is also used to prepare sugar-coating solutions in combination with sucrose.

6.5. STARCH

Nonproprietary Names:

BP : Maize starch, Potato starch, Rice starch, Tapioca starch, Wheat starch.

JP : Corn starch, Potato starch, Rice starch, Wheat starch.

PhEur : Maydis amylum (maize starch), Solani amylum (potatostarch),Oryzae amylum (rice starch), Tritici amylum (wheat starch).

USPNF : Corn starch, Potato starch, Tapioca,Wheat starch.

Synonyms

Amido; amidon; amilo; amylum; Aytex P; C*PharmGel, Fluftex W; Instant Pure-Cote; Melojel; Meritena; Paygel 55; Perfectamyl D6PH; Pure-Bind; Pure-Cote; Pure-Dent; Pure-Gel; Pure-Set; Purity 21; Purity 826; Tablet White.

Chemical Name

Starch

Empirical Formula

$(C_6H_{10}O_5)$ n.

Molecular Weight

50 000–160 000.

Functional Category

Glidant, tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

Physical state

Starch occurs as an odorless and tasteless, fine, white-colored powder comprising very small spherical or ovoid granules.

Typical Properties

Acidity/alkalinity **:** pH = 5.5–6.5

Density (bulk) **:** 0.462 g/cm3

Density (tapped) **:** 0.658 g/cm3

Density (true) **:** 1.478 g/cm3

Solubility

Practically insoluble in cold ethanol (95%) and in cold water.

Stability & Storage Conditions

Dry, unheated starch is stable if protected from high humidity. When used as a diluent or disintegrant in solid-dosage forms; starch is considered to be inert under normal storage conditions. Starch should be stored in an airtight container in a cool, dry place.

Applications

Starch is used as excipients primarily in oral solid-dosage formulations where it is utilized as a binder, diluents, and disintegrant. In tablet formulations, freshly prepared starch paste is used at a concentration of 5–25% w/w in tablet granulations as a binder. Starch is one of the most commonly used tablets disintegrant at a concentration of 3–15% w/w.

Solubility

Freely soluble in acids, chloroform, ethanol, ketones, methanol and water.

Incompatibilities

Thiomerosal adversely affected by the formation of complexes with povidone.

Applications

Primarily used in solid dosage form in tablet povidone solution used as binder in wet granulation processes. It is used as solubilizer in oral and parenteral formulation and has been shown to enhanced dissolution of poorly soluble drug from solid dosage form. It is also used

as coating agent. Also used as suspending, stabilizing, or viscosity increasing agent in a number of topical and oral suspension and solution.

6.7. COLLOIDAL SILICON DIOXIDE

Structural formula **:** SiO_2

Non proprietary name

BP **:** Colloidal anhydrous silica

PhEur **:** Silica colloidal is anhydrica

USP **:** Colloidal silicon dioxide

Synonym

Aerosil, fumed silica, Cab-o-sil, Colloidal silica, Silica anhydride, Silicon dioxide fumed, wacker HDK.

Chemical name

Silica

Molecular weight 60.08

Functional category

Adsorbent, Anticaking agent, Glidant, Suspending agent, Tablet disintegrant, Viscosity increasing agent.

Physical state

It is a light, loose, bluish-white coloured, odorless, tasteless, nongritty, amorphous powder.

Typical properties

Density (bulk) **:** 0.029-0.042 g/cm^3

pH **:** 3.5-4.4 (4% w/v aqueous dispersion)

Stability & Storage condition

It is hygroscopic, but absorbs large quantities of water without liquefying. It should be stored in a well-closed container.

Incompatibilities

Incompatible with diethyl stilbesterol preparations.

Application

It is widely used in pharmaceutical formulations to improve the flow properties of dry powders. It is used as glidant in 0.1-0.5%.

Table No: 5 Different concentration of Colloidal silicon dioxide

Use	Concentration in %
Aerosols	0.5-2.0
Emulsion Stabilizer	1.0-5.0
Glidant	0.1-0.5
Suspending and Thickening agent	2.0-10.0

6.2.8. MAGNESIUM STEARATE

Structural formula **:** $[CH_3 (CH_2)_{16}COO]_2 Mg$

Empirical formula **:** $C_{36}H_{70}MgO_4$

Molecular weight **:** 591.34

Chemical name **:** Octadecanoic acid, Magnesium salt

Non proprietary name

BP **:** Magnesium stearate

JP **:** Magnesium stearate

PhEur **:** Magnesii stearas

USP **:** Magnesium stearate

Synonym

Magnesii stearas, Magnesium octadeconate, Magnesium salt.

Physical state

It is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste.

Functional category

Tablet and capsule lubricant.

Typical properties

Density (bulk)	:	0.159 g/cm^3
Density (tapped)	:	0.286 g/cm^3
Density (true)	:	1.092 g/cm^3
Melting point	:	117-150^{o}c

Solubility

Practically insoluble in ethanol, ether, and water

Slightly soluble in warm benzene and ethanol.

Stability & Storage condition

Magnesium stearate is stable and should be stored in a well closed container in a cool dry place.

Incompatibilities

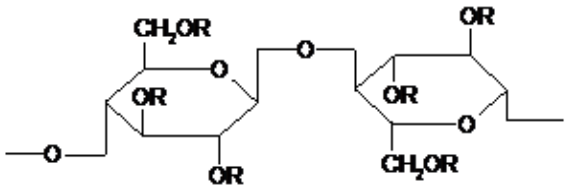
It is incompatible with strong acids, alkalies, and iron salts. It cannot be used in products containing aspirin, vitamins and alkaloidal salts.

Applications

It is widely used in cosmetics, food products and pharmaceutical formulations. It is used as a lubricant in capsule and tablet manufacture at concentration between 0.25-5.0 %.

6.9. HYPROMELLOSE

Structural formula



Where, R is H, CH_3, or $CH_3CH(OH)CH_2$

Molecular weight : 80,000-140,000.

Chemical name : Cellulose-2-hydroxypropyl methyl ether.

Non proprietary name

BP	:	Hypromellose
JP	:	Hydroxypropyl methylcellulose.
USP	:	Hypromellose.

Synonym

Methocel, Metolose, Benecel MHPC, Pharmacoat.

Physical state

White to off-white powder or flakes.

Melting point

Softens at 1308C; chars at 260–2758C.

pH

5.5 – 8.0 for a 1% w/w aqueous solution.

Solubility

It is soluble in cold water but insoluble in chloroform, ethanol (95%), and ether, but soluble in mixture of ethanol and dichloro -methane, mixture of methanol and dichloro -methane, mixture of water and alcohol.

Viscosity

A wide range of viscosity grades are commercially available.

Table No: 6 Different Grades of Hypromellose with its Viscosity

Methocel Grade	Viscosity (m Pa)
K100LV	80-120
K4M	3000-5600
K15M	12000-21000
E4M	3500-5600
E3PREM.LV	2.4-3.6
E5PREM.LV	4-6
E50PREM.LV	40-60
E6PREM.LV	5-7
E15PREM.LV	12-18

Stability & Storage condition

It is a stable material although it is hygroscopic after drying. Ii shoud be stored in a well- closed container, in a cool and dry place.

Applications

It is used as a viscosity control agent, gelling agent, film former, stabilizer, dispersant, lubricant, binder emulsifying agent, and include suspending agent. End applications adhesives and glues, agriculture, building materials, personal care products, detergents and surfactants, paints, printing inks and coatings, pharmaceutical products, polymerization and textiles.

Incompatibility

Incompatible with some oxidizing agents.

6.10. POLY ETHYLENE GLYCOL- 400

Chemical Name **:** α-Hydro-o-hydroxypoly(oxy-1,2-ethanediyl)

Empirical Formula **:** $HOCH_2$ (CH_2OCH_2) mCH2OH

Where, m represents the average number of oxyethylene groups.

Molecular Weight **:** 76.09

Nonproprietary Names:

BP	:	Macrogol
JP	:	Macrogol 400
Ph.Eur	:	Macrogola
USPNF	:	Polyethylene glycol

Synonyms

Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; PEG; PluriolE, polyoxyethylene glycol.

Melting point

59^0C.

Functional Category

Ointment base, plasticizer; solvent, suppository base, tablet and capsule lubricant.

Solubility

Soluble in water, acetone, alcohols, benzene, glycerin, and glycols.

Description

Occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste.

Density

1.11–1.14 g/cm^3 at 25ºC

Stability and Storage conditions

Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, and they do not become rancid. Polyethylene glycols should be stored in well-closed containers in a cool, dry place. Stainless steel, aluminum, glass, or lined steel containers are preferred for the storage of liquid grades.

Incompatibilities

Incompatible with some coloring agents.

Applications

Plasticizer, tablet binder, suspending agent, emulsifying agent, suppository base, disintegrant.

6.11. IRON OXIDE

Empirical Formula: Fe_3O_4.

Synonym

Ferric hydroxide; Ferric hydrate; Ferric oxide hydrated.

Description

Iron oxides occur as yellow, red, black, or brown powder.

Molecular Weight

231.54

Functional category

Colorants

Solubility

Soluble in strong mineral acids, practically insoluble in water.

Melting point

1538^0C.

Density

5.1 g/cm^3.

Stability & Storage

It should be stored in well-closed containers in a cool, and dry place.

Incompatibilities

Iron oxides have been reported to make hard gelatin capsules, brittle at higher temperatures when the residual moisture is 11-12%. This factor affects the use of iron oxides for coloring hard gelatin capsules and will limit that can be incorporated into the gelatin material.

Applications

Iron oxides are widely used in cosmetics, foods, and pharmaceutical applications as colorants and UV absorbers.

6.12. TITANIUM DIOXIDE

Titanium Dioxide is a white, amorphous, odorless, and tasteless powder. Although the average particle size of titanium dioxide powder is less than 1 mm, commercial titanium dioxide generally occurs as aggregated particles of approximately 100 mm diameter.

Synonym **:** Anatase titanium dioxide; Brookite titanium dioxide.

Empirical Formula **:** TiO_2

Molecular Weight **:** 79.88

Melting point **:** 1855^0C

Density (bulk) **:** 0.4–0.62 g/cm^3.

Density (tapped) **:** 0.625–0.830 g/cm^3.

Density (true) **:** 3.8–4.1 g/cm^3.

Applications

Titanium dioxide is widely used in confectionery, cosmetics, foods, in the plastics industry, and in topical and oral pharmaceutical formulations as a white pigment in film-coating suspensions, sugar-coated tablets, and gelatin capsules. Titanium dioxide may also be admixed with other pigments. Titanium dioxide is also used in dermatological preparations and cosmetics such as sunscreens.

7. MATERIALS AND SUPPLIERS

LIST OF MATERIALS

Table No: 7 List of Materials and its suppliers

S. No	Materials	Manufacturers/suppliers
1	Fexofenadine hydrochloride	Vasudha pharma chemical limited
2	Microcrystalline cellulose	Vijlak pharma, india
3	Microcrystalline cellulose 102	Weiming phrmaceuticals, india
4	Pregelatinised starch	Colorcon asia pvt. Ltd
5	Croscarmellose sodium	Minglai chemicals co, ltd
6	Lactose monohydrate	DVM international. Ltd
7	Starch	Maize products
8	Povidone	Namberg india co.
9	Colloidal silicon dioxide	Cabot sanmar
10	Magnesium stearate	Vijlak pharma
11	Hydroxyl propyl methyl cellulose_15Caps	Samsing chemicals
12	Hydroxyl propyl methyl cellulose_E5	Samsing chemicals
13	Polyoxy ethylene glycol_400	Vasudha chemicals pvt ltd
14	Iron oxide red	Neshiel chemical pvt limited
15	Titanium dioxide	BASF

LIST OF INSTRUMENTS

Table no: 8 List of Instrument and its suppliers

S. No	Intruments	Manufacturers/suppliers
1	Elecronic balance	Adventurer Mettler Toleda
2	pH Meter	Lab India
3	FTIR Spectrophotometer 8300	Perkin Elmer
4	HPLC	Shimadzu-corporation, Japan
5	Disintegration tester	Electrolab,ED-21, India
6	Dissolution test apparatus(Disso 2000)	Lab India dissolution test apparatus
7	Friability test apparatus	Electro lab,ET-2, India
8	Bulk density apparatus	Thermonik, Campbel Electronics
9	Melting point apparatus	Lab India
10	Moisture balance	OHAVS moisture balance
11	Vernier calipers	Mitutoyo corps, Japan
12	Hardness tester	Monsanto test apparatus

LIST OF EQUIPMENTS

Table No: 9 List of equipments and its suppliers

S. No	Equipments	Manufacturers/suppliers
1	Humidity chamber	Thermolab India
2	Fluidized bed dryer	Alliance Engineering Company, Bombay
3	8 Station tablet compression machine	Accura, Ahmedabad
4	Coating pan	Air creation India

8. EXPERIMENTAL SECTION

8.1 PREFORMULATION STUDY[41]

Preformulation studies are designed to determine the compatibility of initial excipients with the active substance for a biopharmaceutical, physicochemical and analytical investigation in support of promising experimental formulations. Successful formulations take into account a drug's interactions with the physicochemical properties of other ingredients [and their interactions with each other] to produce a safe, stable, beneficial and marketable product.

The basic purpose of the preformulation activity is to provide a rational basis for the formulation approaches, to maximize the chances of success in formulating an acceptable product and to ultimately provide a basis for optimizing drug product quality and performance. The first step in any formulation activity is careful consideration of a complete physicochemical profile of the active ingredients available, prior to initiating a formulation development activity.

CONTENT OF PREFORMULATION STUDIES:

1. Solubility:

1 part of drug was taken and dissolved in 5 ml of methanol, and found that the drug was freely soluble in methanol. 1 part of drug was taken and dissolved in 10 ml of chloroform or 10 ml of water, and found to be that the drug was slightly soluble in chloroform and water.

2. Melting point:

Required amount of drug was taken in capillary tube, and then the capillary tube was kept in melting point apparatus. The melting point was determined by using LAB INDIA melting point apparatus.

3. Loss on drying (%):

Loss on drying is an expression of moisture content. The loss on drying test is designed to determine the amount of water and volatile matters in a sample, when the sample is dried under specified conditions. The loss on drying of the blend (1g) was determined by using electronic LOD (OHAVS moisture balance)

DRUG EXCIPIENT COMPATIBILITY STUDIES:[42]

Drug-excipient compatibility studies are carried out for designing a chemically stable formulation for clinical and commercial development. Drug excipient compatibility studies are conducted during preformulation to select the most appropriate excipients, to study the compatibility of active ingredients with selected excipients and to prove that the selected excipients are compatible with the active ingredient. The active ingredients and the excipients were mixed in the selected ratios using a mortar and pestle. The mixtures are transferred into glass vials and sealed. The samples were kept at 40ºC±2ºC/75%±5% RH for 4 weeks. The samples were analyzed for physical and chemical incompatibilities.

IR SPECTRAL STUDIES: [43]

KBr pellet technique was followed for this study. In this the sample and the KBr were taken in 1:300 ratio.The mixture of sample and KBr was triturated to make fine powder. The fine powder was made into pellets by using pellitizer. The transparent pellets were placed in the Perkin elmer FT-IR spectrometer and the spectrum was recorded. The FT-IR analysis was done for both Fexofenadine Hydrochloride and also for prepared formulations.The frequencies of the possible peaks of FT-IR spectra of Fexofenadine Hydrochloride should match with the drug - excipients spectra.

Table No: 10 List of Excipients for Preformulation Study

S.No.	INGREDIENT	USE	DRUG-EXCIPIENTS RATIO
1.	Croscarmellose sodium	Disintegrant	1:5
2.	Microcrystalline Cellulose	Diluent	1:10
3.	Starch	Binder/Diluent	1:10
4.	Povidone	Binder	1:0.5
5.	Lactose Monohydrate	Diluent	1:10
6.	Pregelatinized Starch	Binder/Diluent	1:10
7.	Magnesium stearate	Glidant	1:0.25
8.	Titanium dioxide	Opacifier	1:1
9.	Colloidal silicon dioxide	Lubricant	1:0.5
10.	Polyethylene glycol 400	Plasticizer	1:1
11.	Hypromellose E15	Binder/Diluent	1:1
12.	Microcrystalline Cellulose 102	Diluent/ Disintegrant	1:10
13.	Hypromellose E5	Binder/Diluent	1:1

8.2 FORMULATION DEVELOPMENT OF FEXOFENADINE HYDROCHLORIDE 180mg TABLETS

Table No: 11 Formulation development of Fexofenadine Hydrochloride 180mg tablets

S. No	Ingredients		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Fexofenadine Hydrochloride		180	180	180	180	180	180	180	180	180
2	Starch		132	124	_	_	_	_	_	_	_
3	Lactose monohydrate		_	_	180	_	_	_	_	_	_
4	Microcrystalline cellulose	Intra	_	_	_	78	121.5	121.5	220	120	120
		Extra	256	275	144	121.5	_	_	_	_	_
5	Pregelatinsed starch	Intra	_	_	72	180	180	180	30	120	120
		Extra	_	_	_	_	_	72.5	80	50	50
6	Croscarmellose sodium	Intra	20	9	18	18	20	20	18	18	18
		Extra	_	_	_	18	20	20	18	18	18
7	Povidone		6	6	_	_	_	_	15	15	15
8	Microcrystalline cellulose 102 (Extra)		_	_	_	_	72.5	_	30	70	70
9	Colloidal silicon dioxide		_	_	3	_	_	_	3	3	3
10	Magnesium stearate		6	6	3	4.5	6	6	6	6	6
11	Purified water		q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s

Formulation of the Tablet:

The process involved in the tablet formulation by wet granulation method is represented in the schematic method.

Steps involved in the formulation of Fexofenadine Hydrochloride Tablets by Wet Granulation Method:

Weighing of ingredients

↓

Sifting

↓

Dry mixing

↓ Binder

Granulation & Drying

↓ Semi passing (16#)

Milling (Granules passed through Sieve 20#)

↓

Blend

↓

Lubrication

↓

Compression

↓

Coating

↓

Packing

8.3 EVALUATION OF GRANULES AND POWDER BLENDS:[44]

8.3.1. PRE-COMPRESSION PARAMETERS:

The following parameters were determined for the granules (or) powders blends before compression into tablets.

BULK DENSITY:

Bulk density is defined as powder mass divided by its bulk volume without any tapping. Powder bulk density depends primarily on particle size distribution, particle shape, and the tendency of particles to adhere to each other. Some particles may pack loosely, leading to fluffy and light powder, while others may contain smaller particles that site between larger particles to fill the void, leading to dense and heavy powder. Bulk density is often used to calculate the batch size for blender and granulator.

Weighed quantity of granules and powder blends from each formulation was taken in a measuring cylinder and the initial volume of the granules in the measuring cylinder was noted. Bulk density of the granules was calculated by using the following formula.

$$P_b = M/V_b$$

Where,

P_b = Bulk density M = Weight of sample in g,

V_b = Final volume of powder blend in cm^3.

TAPPED DENSITY:

Tapped density of a powder is the ratio of the mass of the powder to the volume occupied by the powder after it has been tapped for a defined period of time. Tapped density was measured by introducing the known quantity of granules into a graduated cylinder and carefully leveling off the granules without compacting it. The cylinder was mechanically tapped by placing on the bulk density apparatus. The volume was measured by tapping the granules for 500 times. Then the tapping was done for 750 times and the tapped volume was noted. The tapped density was calculated by using the following formula:

$$P_t = M/V_t$$

Where,

P_t = Tapped density, M = Weight of the sample in g,

V_t = Tapped volume of powder blend in cm^3

COMPRESSIBILITY INDEX AND HAUSNER'S RATIO:

The compressibility index is a measure of the propensity of a powder to consolidate. As such it is a measure of the relative importance of inter-particle interactions. In a free flowing powder, such interactions are generally less significant and the bulk and tapped densities will be closer in value. For poorer flowing material, there are frequently greater interparticle interactions; bridging between particles often results in lower bulk density and a greater difference between the bulk and tapped densities. These differences in particle interactions are reflected in the compressibility index.The compressibility index of the granules was determined by Carr compressibility index and the Hausner's ratio was calculated by using the formula:

Hausner's Ratio = Tapped density / Bulk density.

Carr's index (%) = [(TD-BD) / TD] x100.

Where,

TD = Tapped density, BD = bulk density.

Table No: 12 Scale of flowability

Flow Character	Compressibility Index (%)	Hausner's Ratio
Excellent	< 10	1.00 – 1.11
Good	11 – 15	1.12 – 1.18
Fair	16 – 20	1.19 – 1.25
Passable	21 – 25	1.26 – 1.34
Poor	26 – 31	1.35 – 1.45
Very Poor	32 -37	1.46 – 1.59
Very, Very Poor	> 38	> 1.60

8.3.2. POST COMPRESSION PARAMETERS:[45]

The tablet was evaluated for its parameters like hardness, thickness, friability, weight variation, and assay and *in-vitro* release studies.

APPEARANCE:

The tablets should be free from cracks, depressions, pinholes etc. The surface of the tablets should be smooth. The tablets were examined externally under a biconvex lens for surface cracks, depressions and pinholes.

THICKNESS:

The thickness of a tablet can vary without any change in its weight. This is generally due to the difference of density of granules, pressure applied for compression and the speed of compression. The thickness of a tablet can be determined with the help of vernier caliper or screw guage. Five tablets from each batch were used, and average values were calculated**.** The thickness was denoted in millimeter.

HARDNESS:

Hardness or tablet crushing strength is the force required to break a tablet in a diametric compression, was measured using Monsanto tablet hardness tester. The values were expressed in Kg/cm^2. The hardness was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester, at this point reading should be zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured.

FRIABILITY:

Specified number of tablets are weighed and placed in the tumbling chamber of the friabilator and rotated for four minutes at a speed of 25 Rpm.. During each revolution the tablets fall from a distance of six inches to undergo shock. After 100 revolutions the tablets are dusted and again weighed and the loss in weight indicates the friability.

Finally can be determined by the following formula

$$F = W1 - W_2 / W_1 \times 100$$

Where,

W_1 = Weight of the tablets before test

W_2 = Weight of the tablets after test

WEIGHT VARIATION TEST:

20 tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated. The tablets meet the USP specifications if not more than two tablet are outside the percentage limit and if no tablet differs by more than two times the percentage limits.

%Deviation = Individual Weight – Average Weight / Average Weight × 100

Table no: 13 Weight variation tolerance for tablets

AVERAGE WEIGHT OF TABLETS	AVERAGE WEIGHT OF TABLETS
80mg or less	±10%
More than 80mg and less than 250mg	±7.5%
250mg or more	±5%

DISINTEGRATION TEST:

The *in-vitro* disintegration test was carried out at 37°±2°C in 900ml of distilled water. The *in-vitro* disintegration time of 6 tablets from each formulation were determined using disintegration test apparatus. One tablet was placed in each of the six tubes of the apparatus containing distilled water. One disk was added to each tube. The time taken in minutes for complete disintegration of the tablet with no mass remaining in the apparatus was noted.

ASSAY:

Chromatographic Condition:

Column : 4.6-mm×25 cm; 5-µm packing L11.
Flow Rate : 1.5 ml/min
Column Temperature : 35ºC
Detector : UV 220 nm
Inj. Volume : 20 µL
Mobile Phase: Buffer : Acetonitrile (9:16)

Preparation of acid solution:

Measure 17 ml of Glacial acetic acid in 1000 ml standard volumetric flask and the volume is produced with distilled water. From this 100 ml solution was pipetted out in a 1000 ml volumetric flask and the volume is made up using distilled water.

Preparation of Buffer:

Prepare 15 ml mixture of acetonitrile and triethylamine (1:1) and make upto 1000 ml with acid solution. Adjust the pH to 5.25 using ortho phosphoric acid.

Diluent : Acetonitrile and Acid solution (300:100)

Mobile phase : Acetinitrile and Buffer solution (432:768)

Preparation of Standard Stock Solution: (0.25mg/ml)

Weigh accurately 25mg of Fexofenadine Hydrochloride in a 100ml volumetric flask. Add 20 ml diluent and sonicate for 30mins then make upto the volume using diluent (Acetonitrile and Acid solution).

Preparation Standard solution:

Pipette out 5ml from the Standard stock solution in a 100ml volumetric flask and make upto the volume using mobile phase (Acetonitrile and Buffer solution)

Preparation of Sample Stock Solution: (0.018mg/ml)

Weigh accurately 180mg of crushed tablet (equivalent to 600 mg of fexofenadine Hydrochloride) in a 100ml volumetric flask. Add 20 ml Acid solution sonicate for about 30mins. Then add 80 ml of Acetonitrile, and sonicate for about 60mins, dilute with diluent to volum, and filter.

Sample solution:

Pipette out 5ml of filtrate in a 50ml volumetric flask and make upto the volume using diluents. From this 5ml was pipetted out in a 50ml volumetric flask and make upto the volume using mobile phase (Acetonitrile and buffer solution).

Procedure:

1.5ml/min Sample is injected into the HPLC instrument and it is allowed to run for 10 minutes and the schematic representation graph is plotted from the instrument. The area value was obtained from the graph and amount of drug present in the formulation was calculated using the following formula.

Amount of drug present = sample area/standard area × standard weight/100 × 5/100 ×100/Sample weight × dilution factor × average weight of the tablet.

***IN-VITRO* DRUG RELEASE STUDIES:**

In vitro test for drug release serve two important functions, however. First, data from such tests are required as a guide to formulation during the development stage, prior to clinical testing. Second, in vitro testing is necessary to ensure batch-to-batch uniformity in the production of a proven dosage form. Digital tablet dissolution test apparatus with paddle is used for the *invitro* dissolution studies of tablets.

Preparation of 0.001N Hydrochloric Acid Buffer: (Dissolution medium)

Measure 8.5ml of hydrochloric acid in 1 liter volumetric flask and make up the volume using purified water. Pipette out 10 ml of the above solution in a 1 liter volumetric flask and make up the volume using purified water.

Preparation of solution A (Buffer solution):

Weigh accurately 1.0g of monobasic sodium phosphate, 0.5g of sodium perchlorate, and 0.3 ml of concentrated phosphoric acid in 300ml of water.

Mobile phase : Acetonitrile and Buffer solution (7:3).

Preparation of standard solution:

Weigh accurately 20mg of Fexofenadine Hydrochloride in a 100ml volumetric flask, add 5ml of methanol and sonicate for 15mins, and make upto volume with dissolution medium.

Procedure:

The *invitro* dissolution test is carried out in 0.001N Hydrochloric acid using Digital tablet dissolution test apparatus. The Fexofenadine tablets are subjected to dissolution testing using rotating paddle apparatus with a speed of 50 rpm in 900ml of dissolution medium. Six tablets were used in each test. A temperature of 37±0.5°C is maintained throughout the experiment. A graph is plotted using time (in X-axis) against percent drug release (in Y-axis).

Sample is injected into the HPLC instrument and it is allowed to run for 10 minutes and the schematic representation graph is plotted from the instrument. The area value was obtained from the graph and amount of drug released from the formulation calculated by the formula below

Percentage of drug released = $\frac{Sample\ area}{Standard\ area} \times \frac{Standard\ weight}{100} \times \frac{900}{600} \times 100$

8.4. PROCEDURE FOR FILM COATING SOLUTION:

Equipment specifications:

Coating technique	: Pan coating
Capacity of pan	: 3kg
Size of pan	: 18 inch
Pan speed	: 18 rpm
Solvent system used	: water (aqueous solvent base coating)
Air pressure	: 1.0 bar
Nozzle size	: 1.0mm

Table No: 14 Ingredients used for Film coating

S.No	INGREDIENTS	QUANTITY FOR 200 TABLETS (in gm)
1	Hypromellose E15	5.68
2	Hypromellose E5	3.78
3	Povidone	1.02
4	Polyethylene glycol 400	7.88
5	Titanium dioxide	4.20
6	Colloidal silicon dioxide	1.46
7	Iron oxide	0.03
8	Purified water	176 ml

Preparation of coating solution:

Specified quantity of hot water was added to Hypromellose E15 and using mechanical stirrer mixed it. Hypromellose E5 was mixed with colloidal silicon dioxide and added to the above mixture and mixed using mechnical stirrer for 10 or 15 minutes. Povidone was added to the above mixture. Finally Titanium dioxide and iron oxide red were mixed separately with little quantity of water and added to the above mixture. This solution was used as coating solution for Fexofenadine hydrochloride.

8.4.1. EVALUATION OF FEXOFENADINE HYDROCHLORIDE FILM COATED TABLETS:

The film-coated tablets were evaluated for the following parameters weight variation test, disintegration, assay, *invitro* drug release studies and stability testing studies.

8.5. STABILITY STUDY: [46]

Fexofenadine Hydrochloride film coated tablets were packed in blister package and short-term stability studies were carried out in two different conditions (40^0C/75% RH and 30^0C/65% RH). The film-coated tablets maintained at 40^0C/75% RH were evaluated every month regularly. The tablets maintained at 30^0C/65% RH were evaluated after three months. This short term stability studies were used for evaluating various parameters such as Description, Disintegration time, Assay, and drug release studies.

9. RESULTS AND DISCUSSION:

9.1. PREFORMULATION STUDY:

1. Appearance: white to off-white crystalline powder

2. Solubility:

Table No: 15 Solubility of Fexofenadine Hydrochloride

S. No	Solvents	Solubility of Drug
1.	1 Part in 5 part Methanol	Freely soluble in methanol
2.	1 Part in 10 part of Chloroform and water	slightly soluble in chloroform and water

3. Melting point: 142.5º C

4. Loss on drying (%): 1.93%

PHYSICAL INCOMPATIBILITY STUDY:

Table No: 16 Results of physical incompatibility Studies

EXCIPIENTS USED	INITIAL	FINAL40ºC±2ºC/75 %±5%RH(4 weeks)	REMARKS
Lactose monohydrate	White powder	No color change	It can be used in formulation
Microcrystalline cellulose	White powder	No color change	It can be used in formulation
Croscarmellose sodium	White powder	No color change	It can be used in formulation
Starch	White powder	No color change	It can be used in formulation
Hypromellose E15	White powder	No color change	It can be used in formulation
Hypromellose E5	White powder	No color change	It can be used in formulation
Povidone	White powder	No color change	It can be used in formulation
Polyethylene glycol 400	White powder	No color change	It can be used in formulation
Titanium Dioxide	White powder	No color change	It can be used in formulation
Magnesium stearate	White powder	No color change	It can be used in formulation
Colloidal silicon dioxide	White powder	No color change	It can be used in formulation
Pregelatinized Starch	White powder	No color change	It can be used in formulation

CHEMICAL INCOMPATIBILITY STUDY:

Table No: 17 Results of chemical incompatibility studies

Wave Number (cm^{-1})	Functional Group
2960-2850	C-H Streching (alkane)
1700-1725	C=O Streching (acid)
1200-1500	O-H Bending (alcohol)
1500-1700	N-H Bendig

FTIR SPECTRAL STUDIES FOR API AND EXCIPIENTS

Fig No: 1 FTIR Spectrum of Fexofenadine Hydrochloride

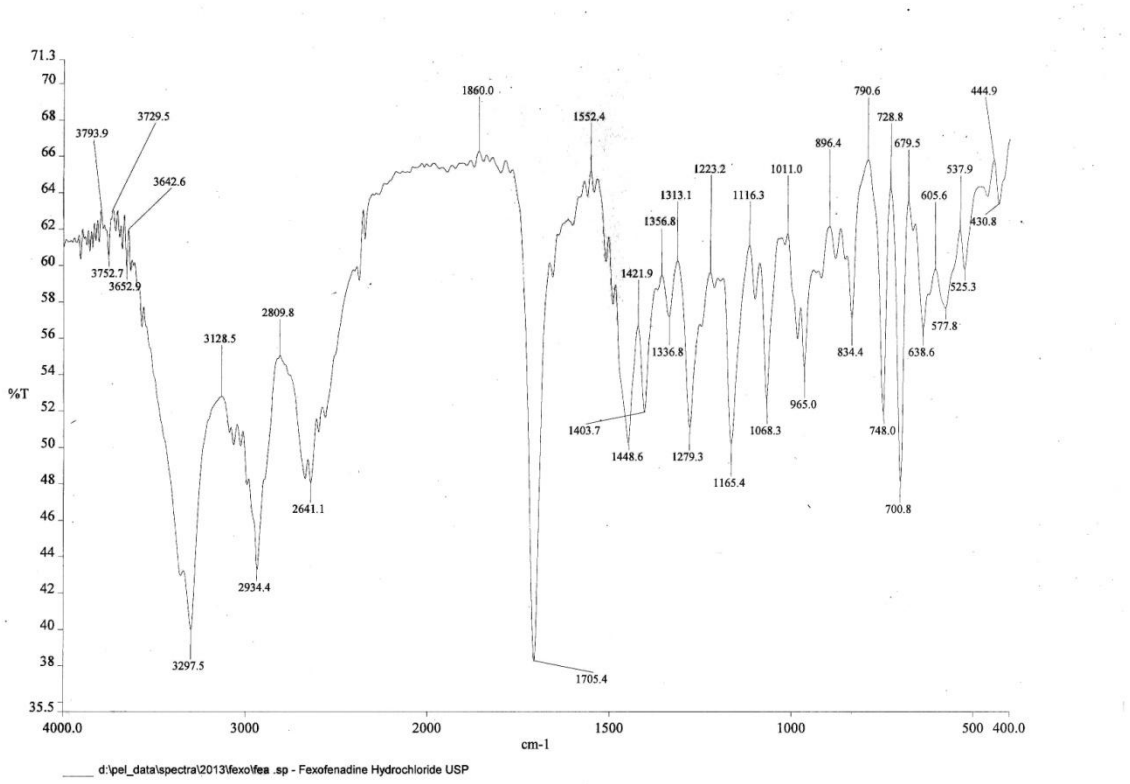


Fig No: 2 FTIR Spectrum Of Fexofenadine Hyddrochloride+ microcrystalline cellulose

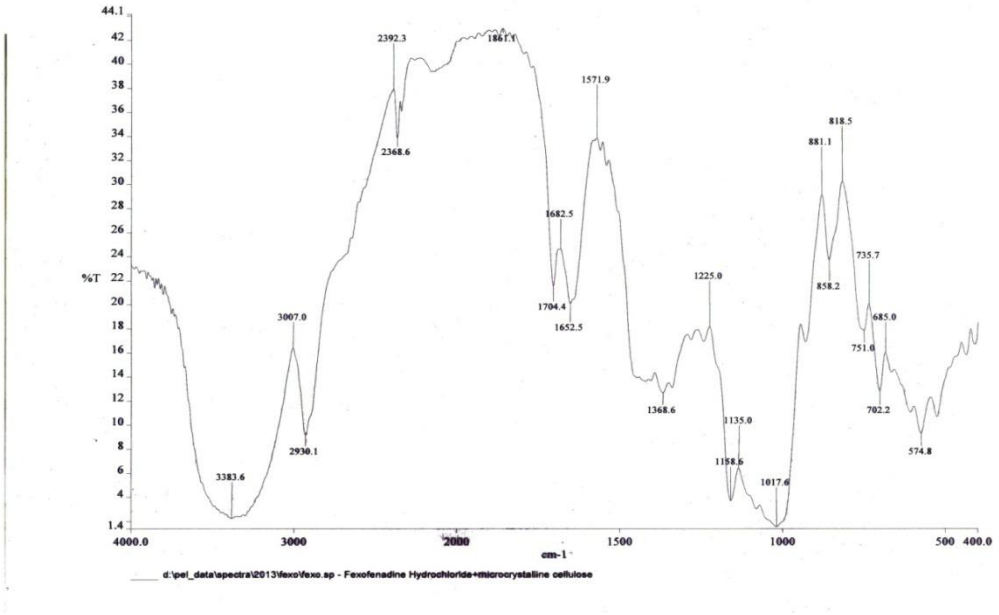


Fig No: 3 FTIR Spectrum Of Fexofenadine Hyddrochloride+Pregelatinised starch

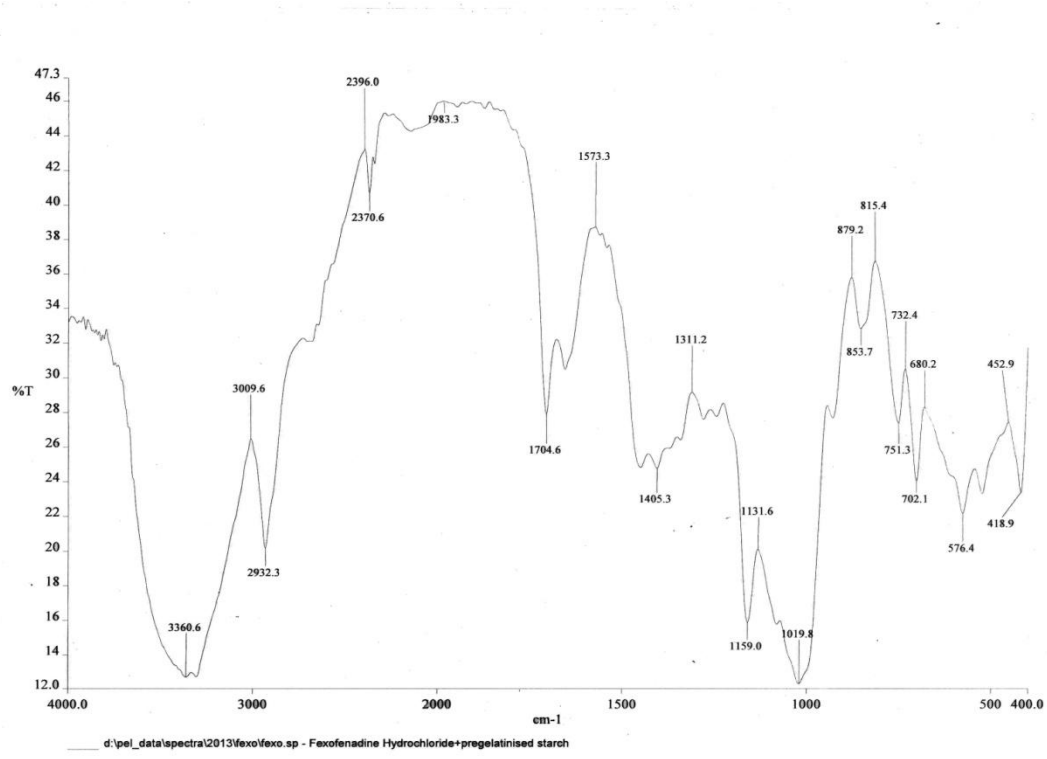


Fig No: 4 FTIR Spectrum Of Fexofenadine Hyddrochloride+ Croscarmellose sodium

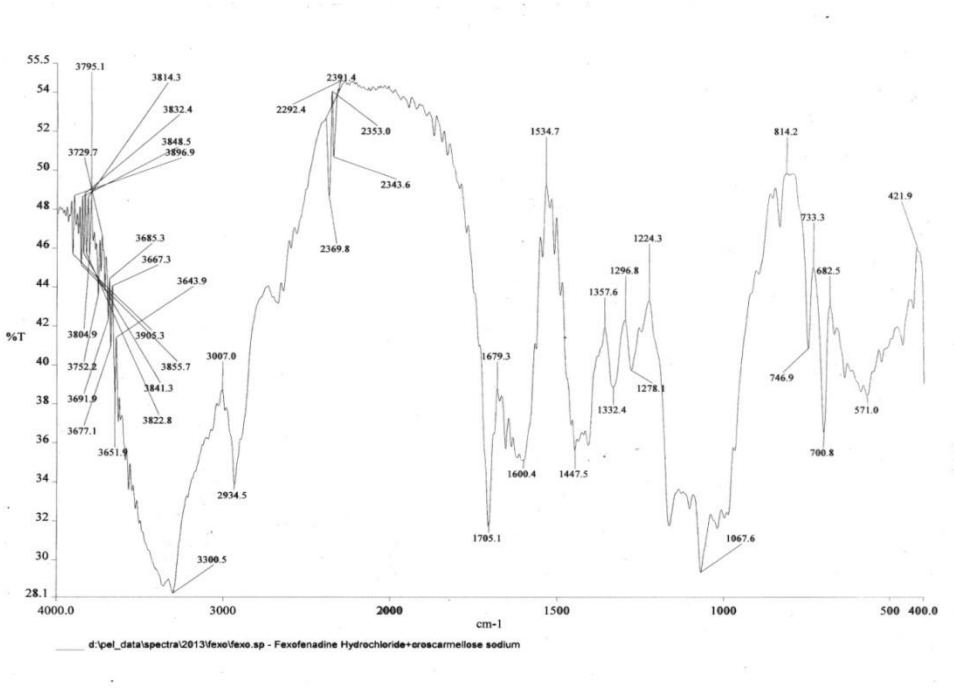


Fig.no. 5 FTIR spectrum of Fexofenadine Hyddrochloride+ colloidal silicon dioxide

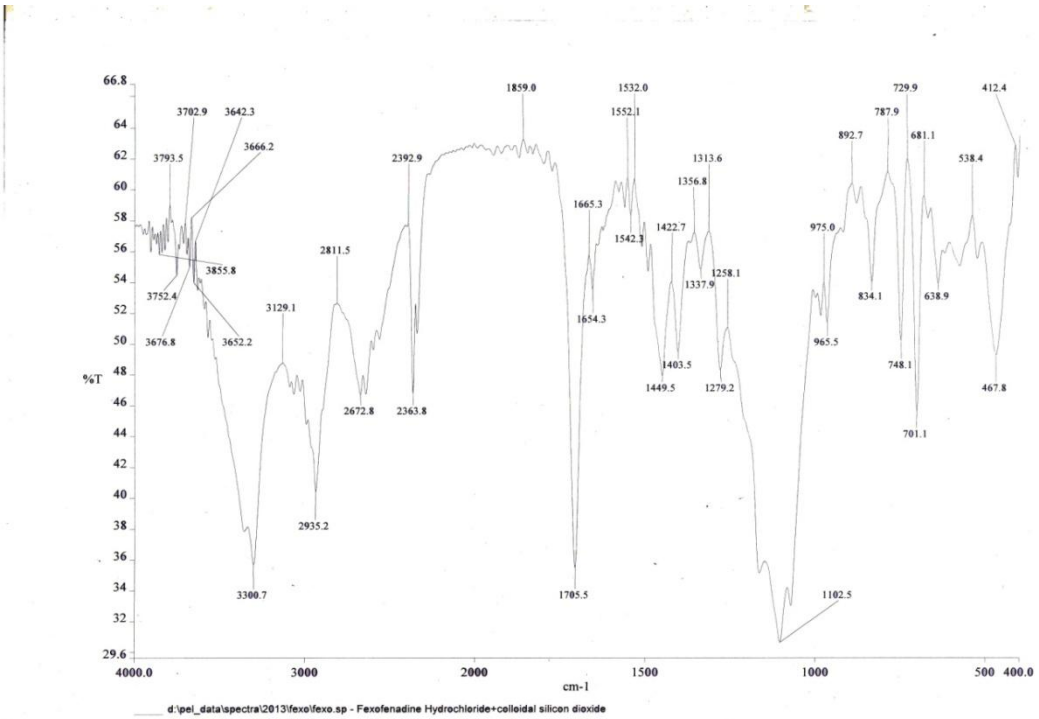


Fig No: 6 FTIR Spectrum Of Fexofenadine Hyddrochloride+magnesium stearate

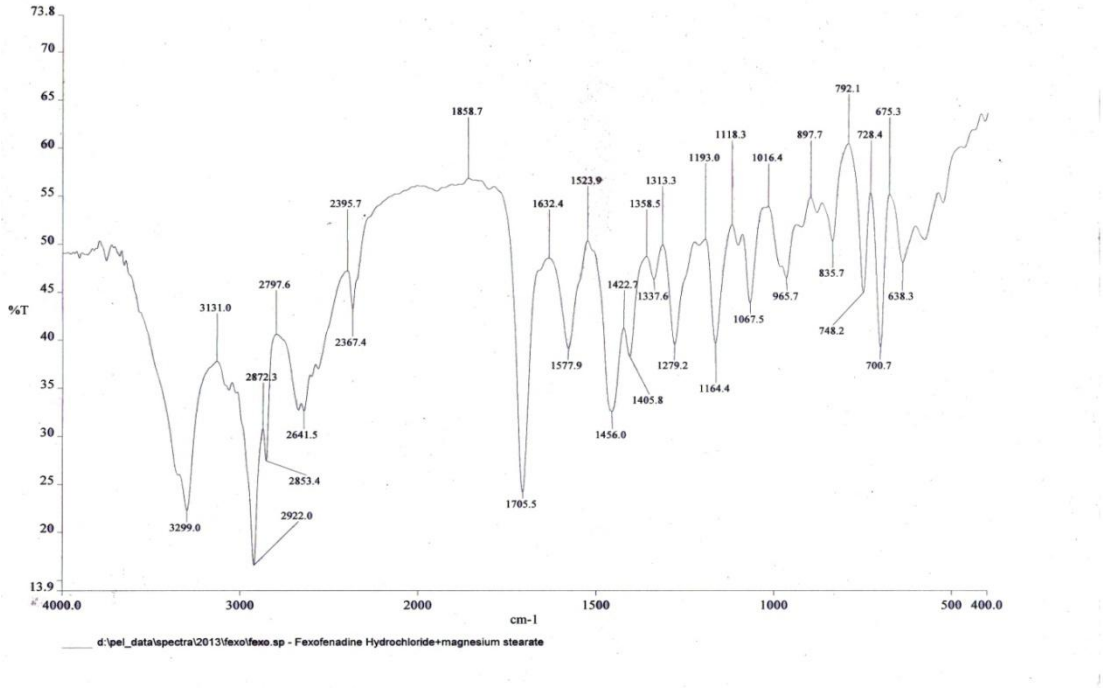


Fig No: 7 FTIR Spectrum Of Fexofenadine Hyddrochloride+ Povidone

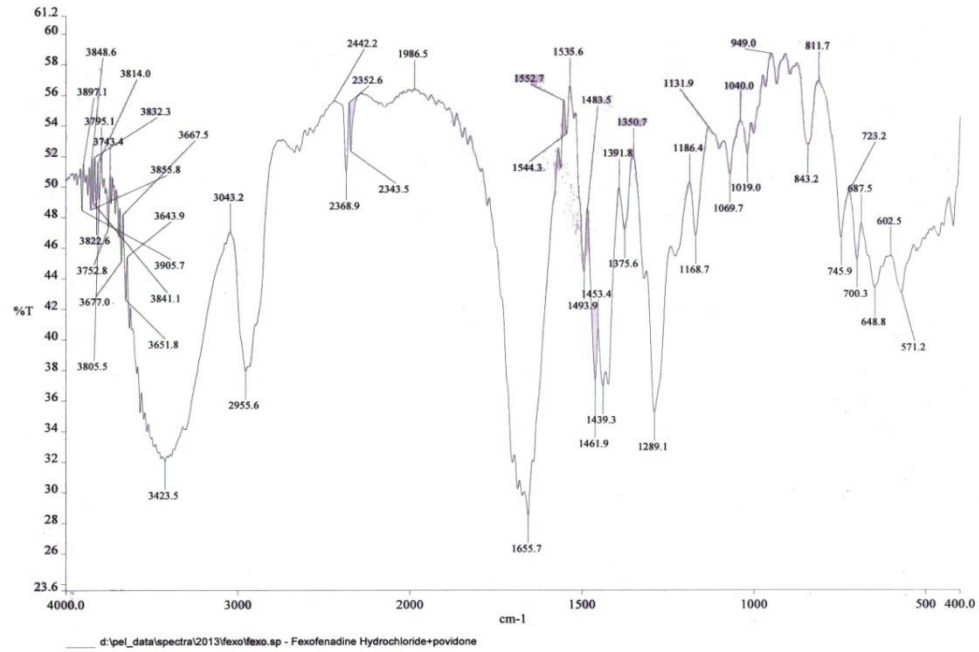
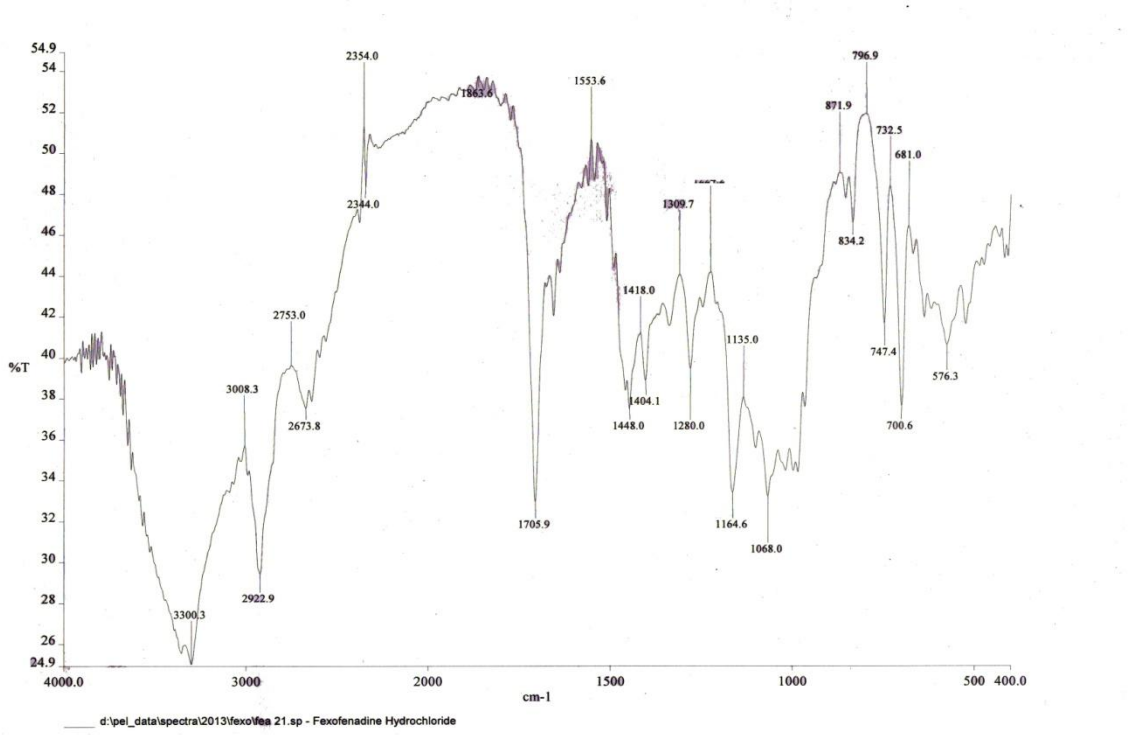


Fig No: 8 FTIR Spectrum Of Fexofenadine Hyddrochloride+ entire all excipients



9.2. PRECOMPRESSION STUDY:

Table no: 18 Results of precompression studies

S. No	Formulation code	Bulk density(g/ml)	Tapped density(g/ml)	Carr's index (%)	Hausner's ratio (%)	Moisture content (%)
1	**F-1**	0.546	0.643	15.08	1.17	2.79
2	**F-2**	0.513	0.604	15.06	1.17	2.26
3	**F-3**	0.536	0.608	11.84	1.13	1.38
4	**F-4**	0.443	0.513	13.64	1.15	3.59
5	**F-5**	0.490	0.561	12.65	1.14	2.77
6	**F-6**	0.478	0.549	12.93	1.14	2.76
7	**F-7**	0.421	0.492	14.43	1.16	3.80
8	**F-8**	0.529	0.599	11.68	1.13	4.16
9	**F-9**	0.557	0.627	11.16	1.12	3.68

POST COMPRESSION STUDY:

Table No: 19 Results of post compression studies

Formulation code	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Average Weight variation(mg)	Disintegration Time	
					Time in seconds	
					With disc	Without disc
F-1	5.72±0.01	11.5±0.08	0.28	598.8±1.01	121±1.2	218±1.32
F-2	5.76±0.03	11.25±0.1	0.22	599.61±1.12	119±1.1	131±1.26
F-3	5.76±0.03	11.42±0.2	0.21	601.10±0.24	99±1.2	102±1.76
F-4	5.80±0.04	10.5±0.42	0.26	599.98±1.02	33±1.3	35±1.36
F-5	5.72±0.06	10.5±0.35	0.15	602.25±1.01	37±1.5	41±2.67
F-6	5.78±0.02	9.55±0.22	0.18	600.20±1.07	34±1.5	35±2.2
F-7	5.74±0.04	10.5±0.05	0.10	600.16±2.22	48±1.47	35±1.21
F-8	5.77±0.03	9.50±0.28	0.18	600.5±1.46	31±2.13	28±1.13
F-9	5.71±0.06	9.50±0.3	0.12	599.1±1.28	38±1.15	30±1.72

The Average weight, Thickness, Hardness values are expressed as mean ± SD n=5.

The disintegration mean ±SD n=6

Fig No: 9 Comparison of Thickness for formulation of F1-F9

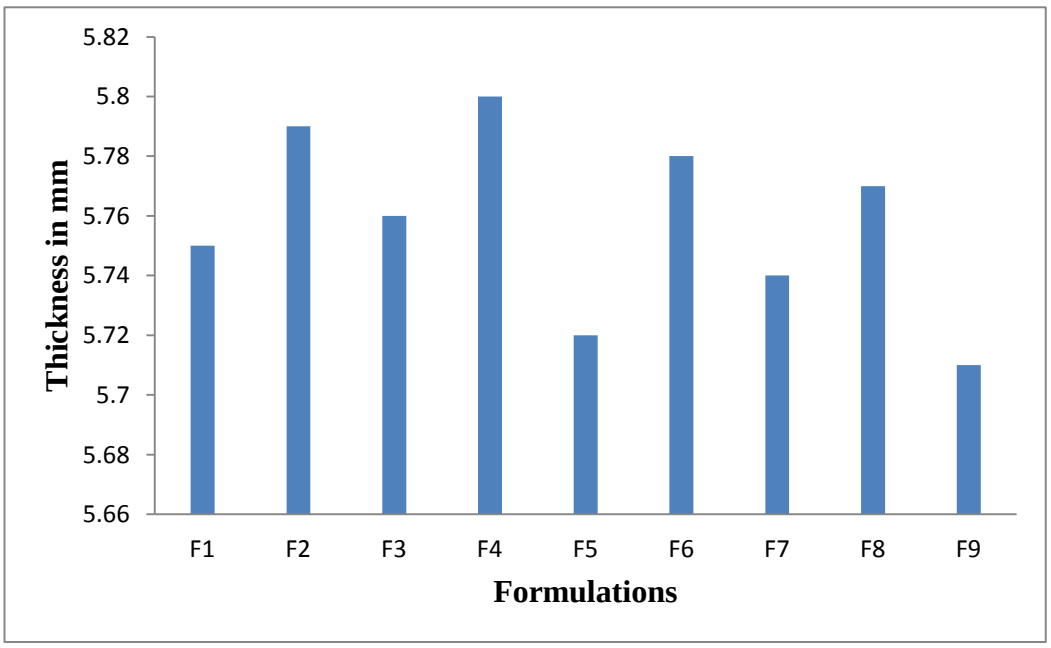


Fig No: 10 Comparison of Hardness for formulation of F1-F9

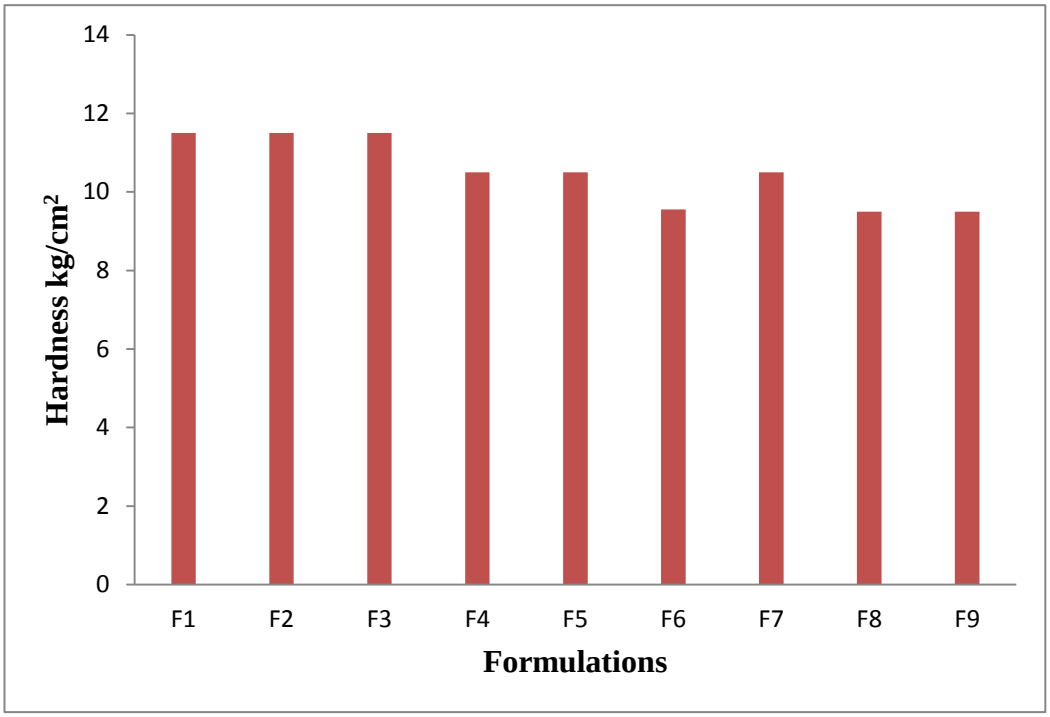


Fig No: 11 Comparison of Friability for formulation of F1-F9

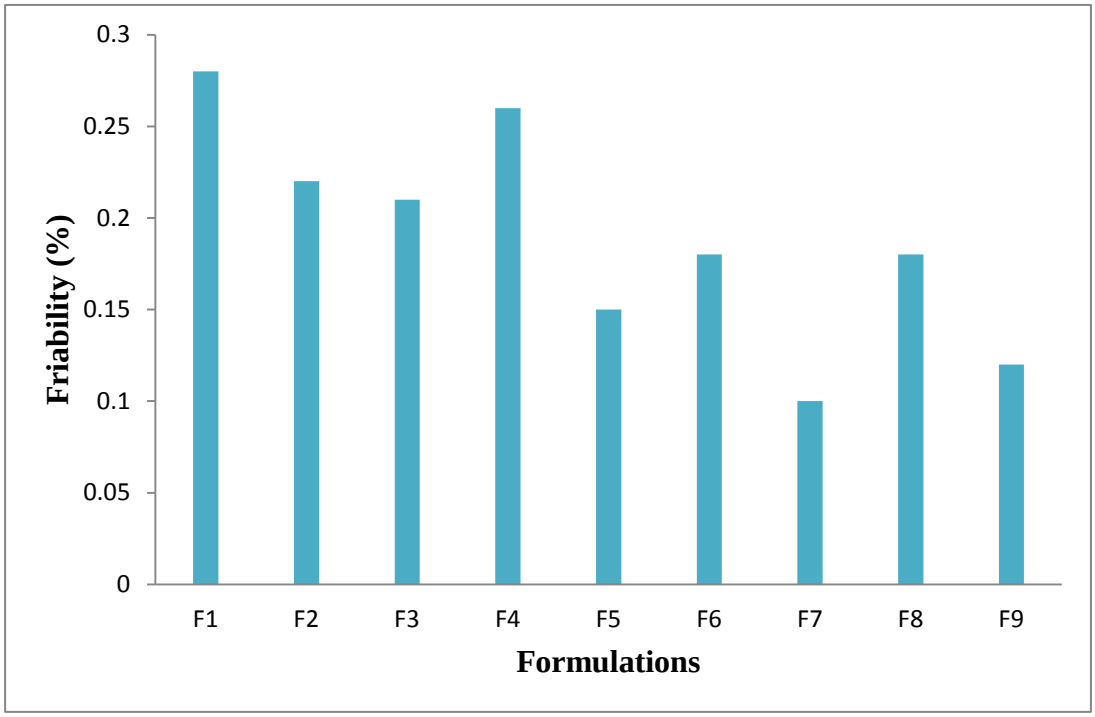
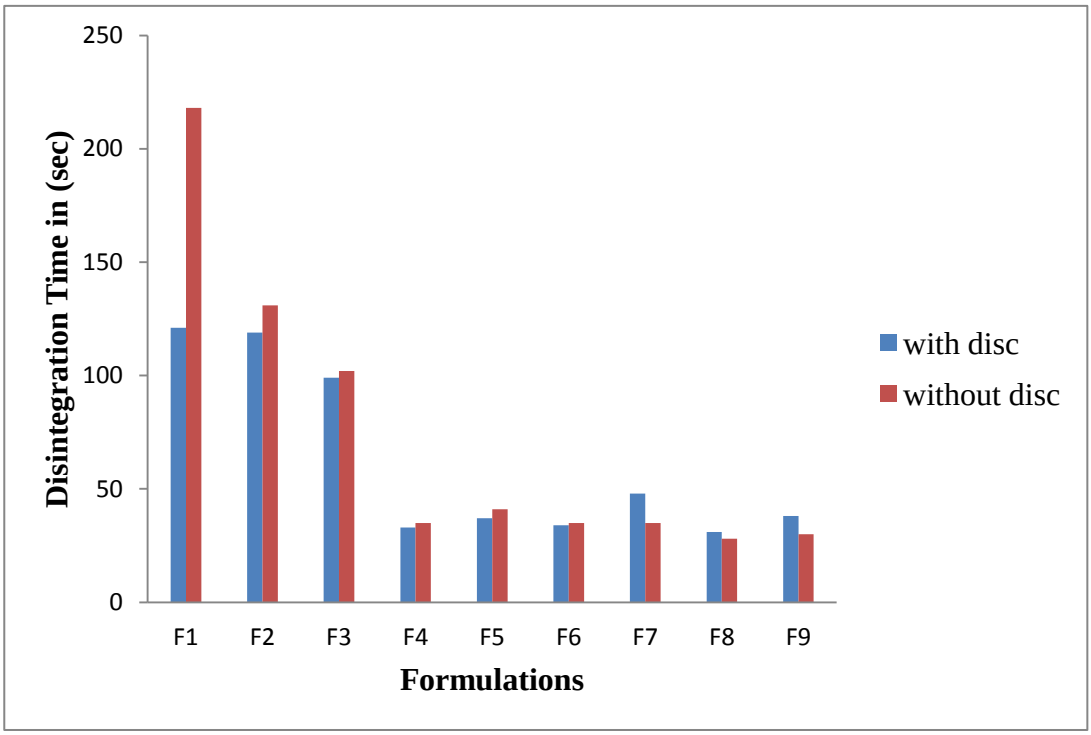


Fig No: 12 Comparison of Disintegration Time for formulation of F1-F9



9.4. ASSAY:

HPLC CHROMATOGRAM FOR ASSAY

Fig No:13 Assay Blank chromatogram

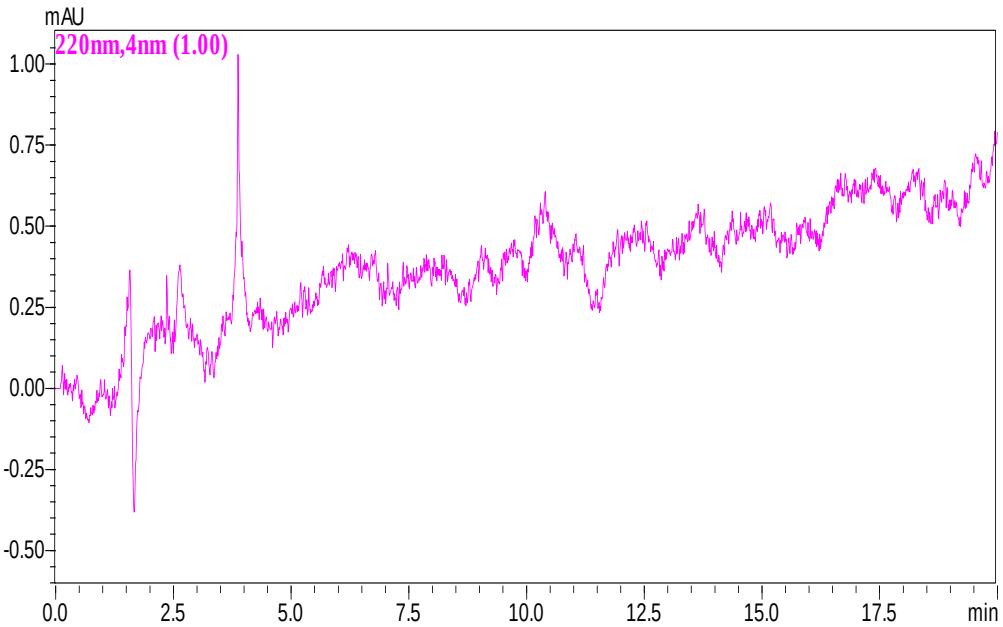


Fig No: 14 Assay standard chromatogram

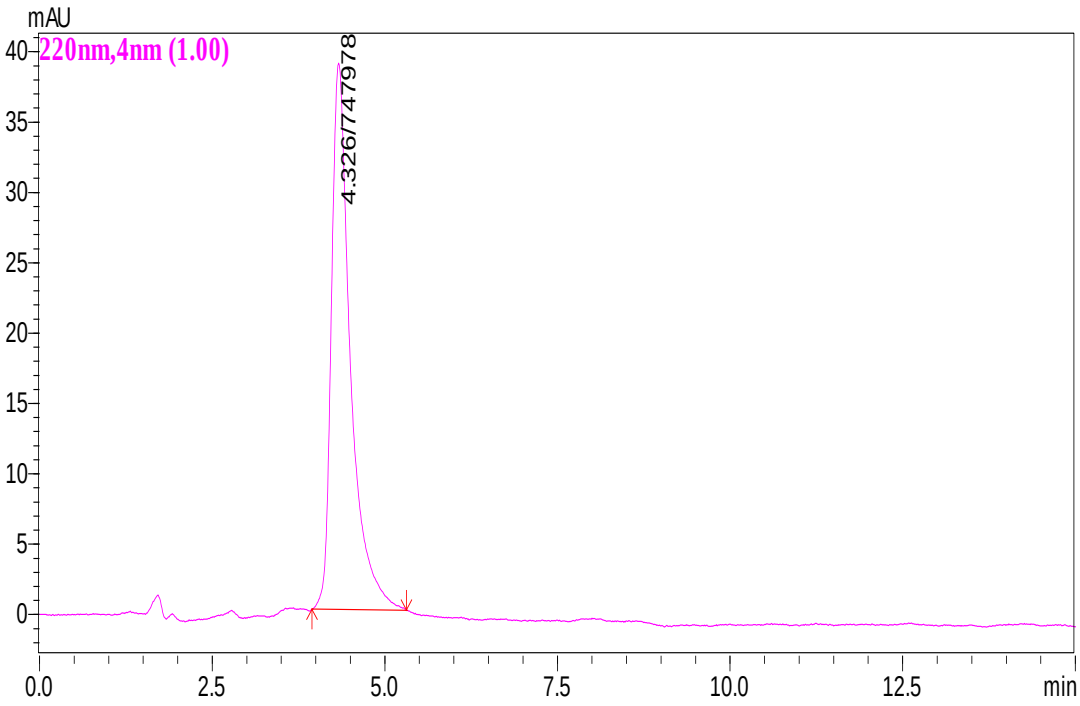
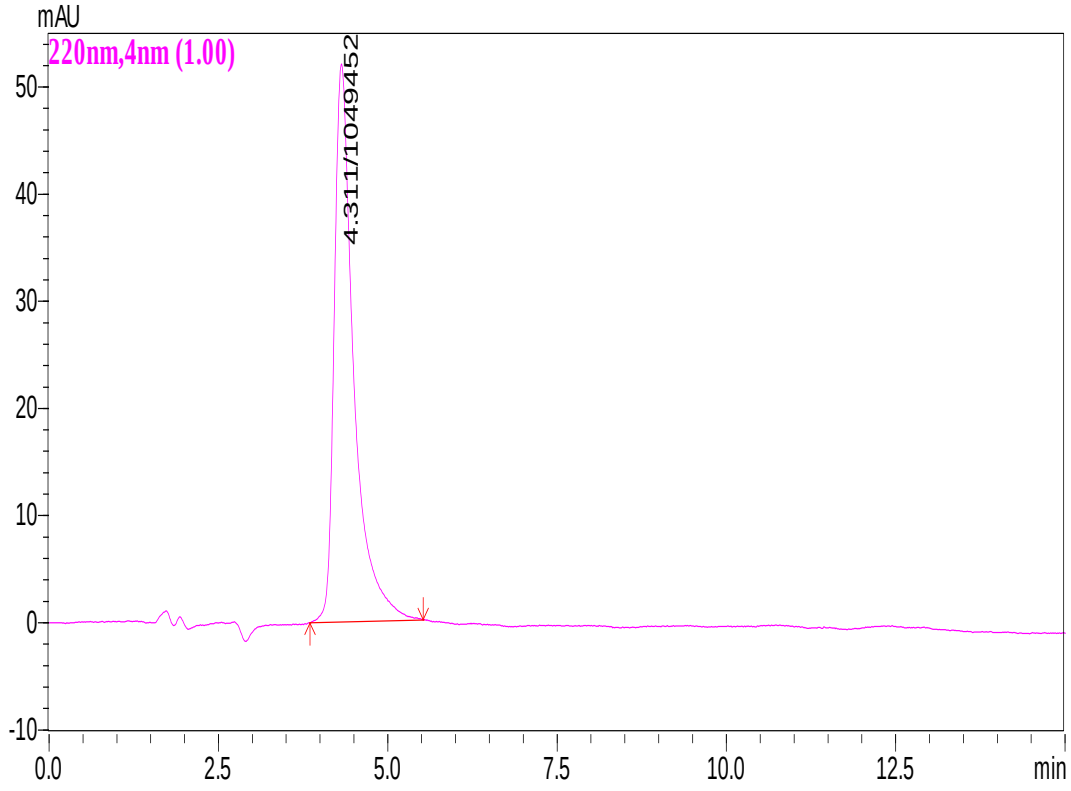


Fig No:15 Assay Sample chromatogram



ASSAY OF FEXOFENADINE HYDROCHLORIDE UNCOATED TABLETS:

Table No: 20 Assay of fexofenadine hydrochloride uncoated tablets

S. No	Formulation code	Assay (%)
1	**F-1**	98.77
2	**F-2**	99.33
3	**F-3**	99.25
4	**F-4**	100.06
5	**F-5**	100.56
6	**F-6**	99.05
7	**F-7**	99.98
8	**F-8**	100.68
9	**F-9**	100.78

9.5. DISSOLUTION STUDY

HPLC CHROMATOGRAM FOR DISSOLUTION:

Fig No: 16 Dissolution Blank chromatogram

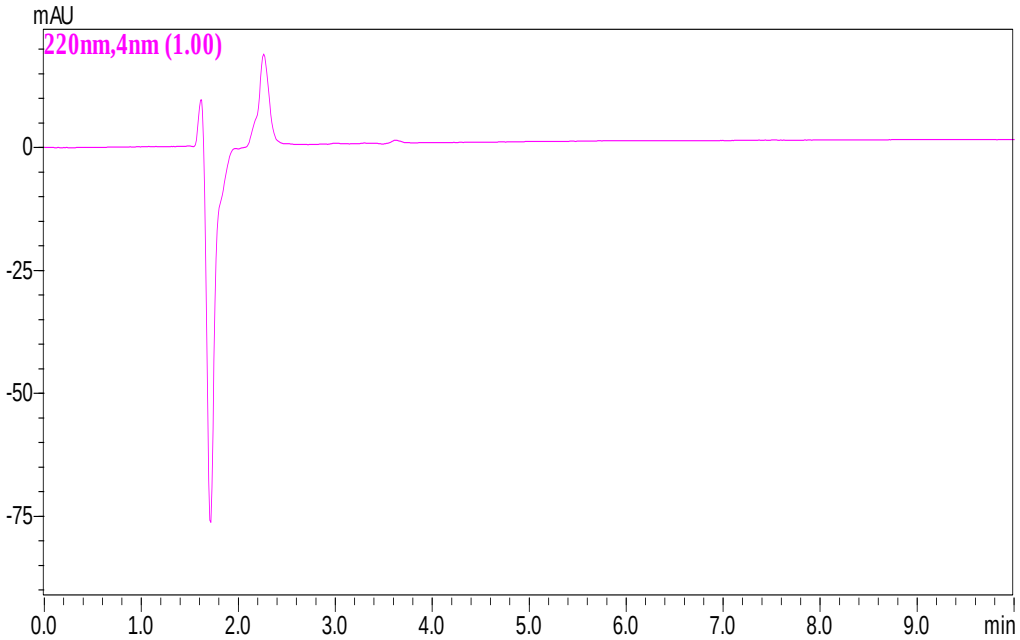


Fig No: 17 Dissolution Standard Chromatogram

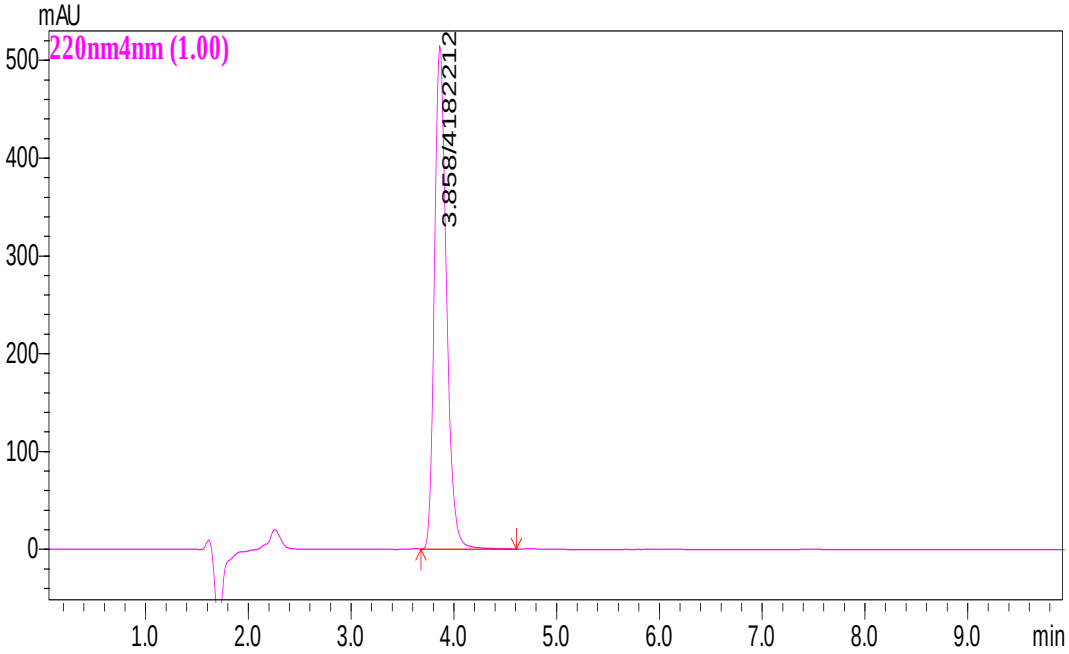


Fig No:18 Sample chromatogram dissolution 10min

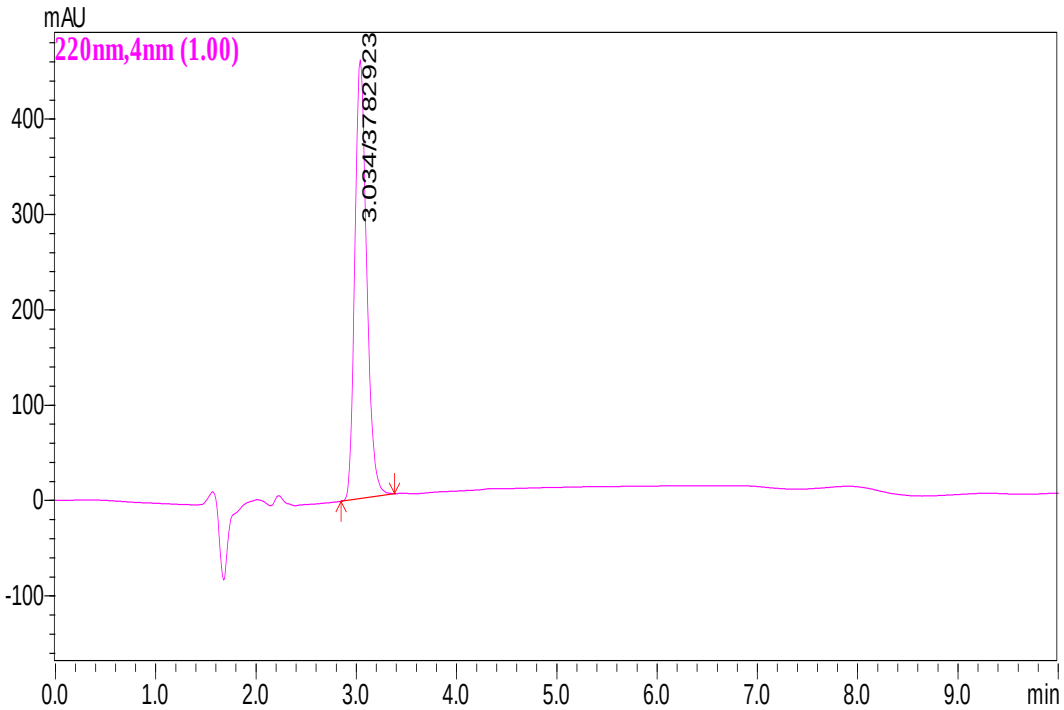
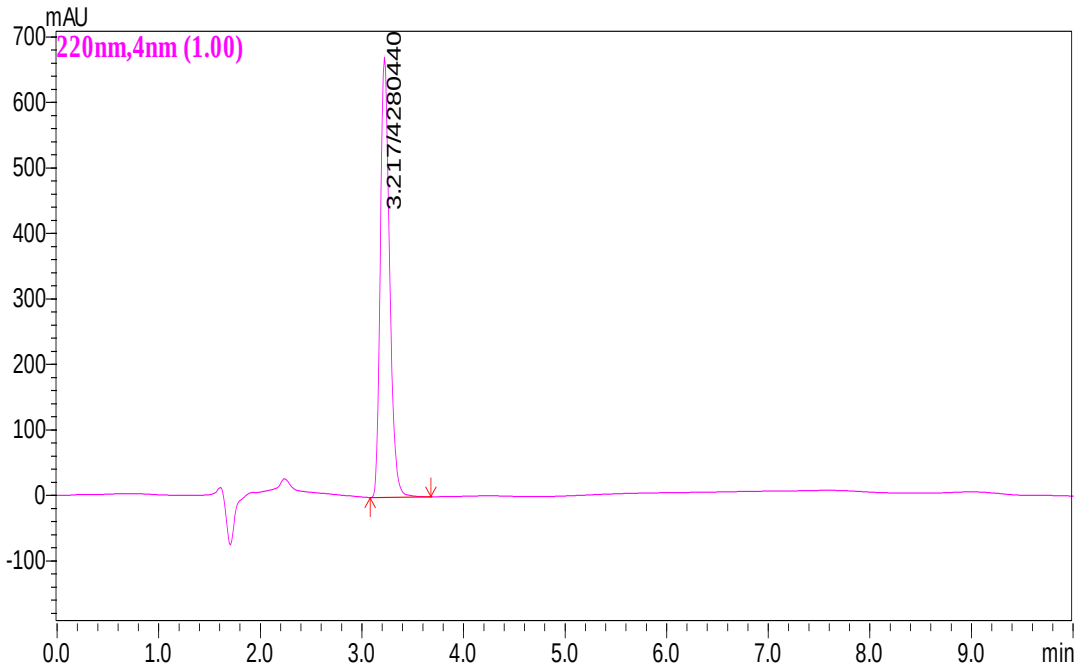


Fig No: 19 Sample chromatogram 30min



IN-VITRO DISSOLUTION OF FEXOFANADINE HYDROCHLORIDE UNCOATED TABLET -180mg

Table No: 21 In-vitro dissolution of fexofanadine hydrochloride uncoated tablet -180mg

S. No	Formulation code	% of Drug release	
		10 minutes	30 minutes
1	F1	69.28	75.67
2	F2	61.08	76.38
3	F3	67.66	80.32
4	F4	68.59	85.56
5	F5	74.95	85.08
6	F6	70.70	85.14
7	F7	81.37	86.07
8	F8	89.77	91.81
9	F9	91.52	96.25

Fig No: 20 Comparison of Dissolution profile of F1-f9

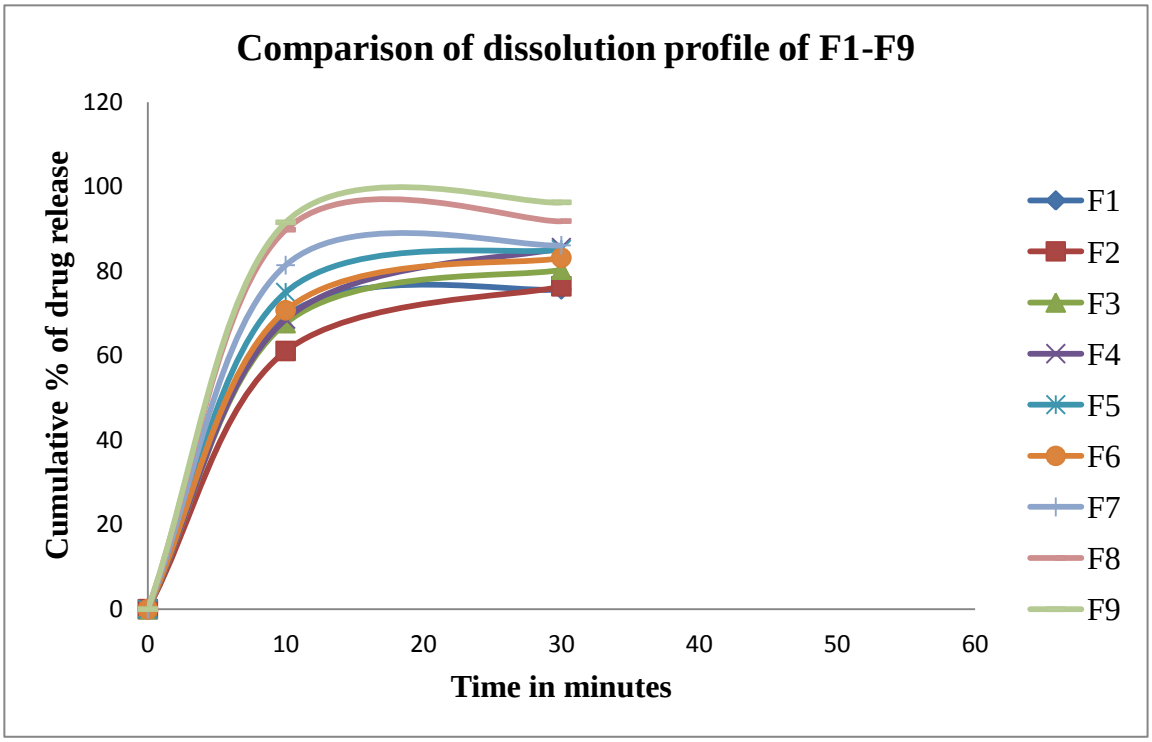


Fig No: 21 Comparison of Dissolution profile of F1-F3

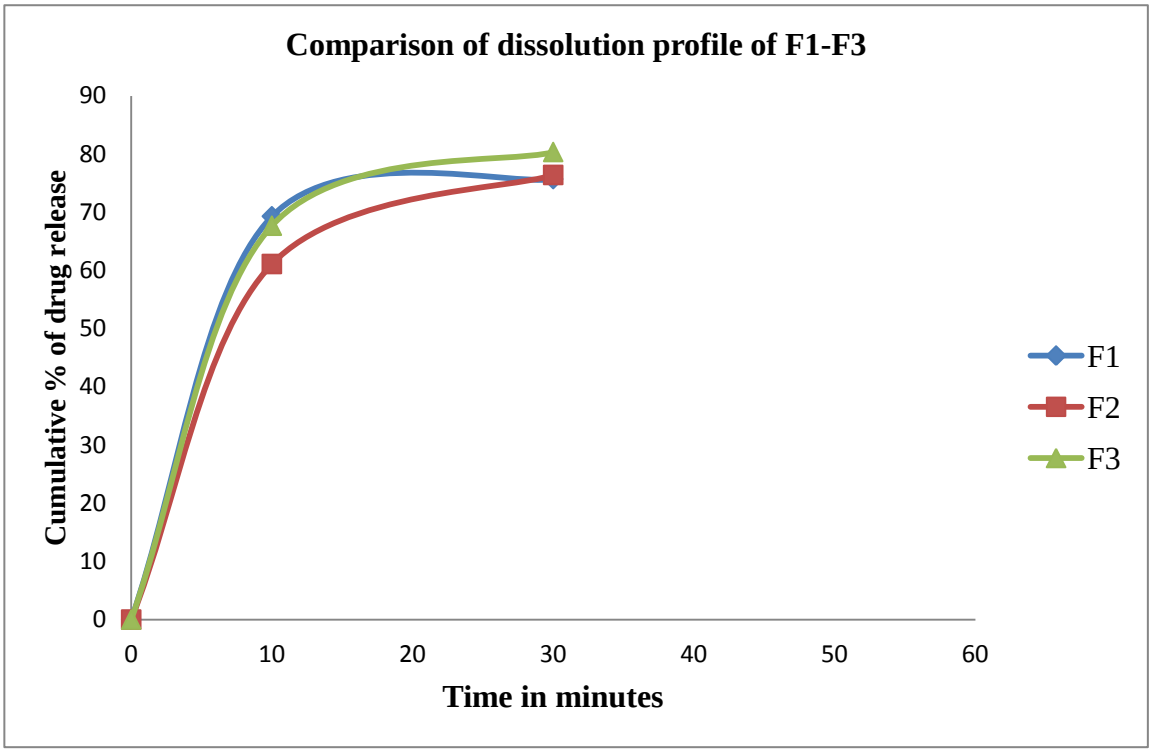


Fig No: 22 Comparison of Dissolution profile of F4-F6

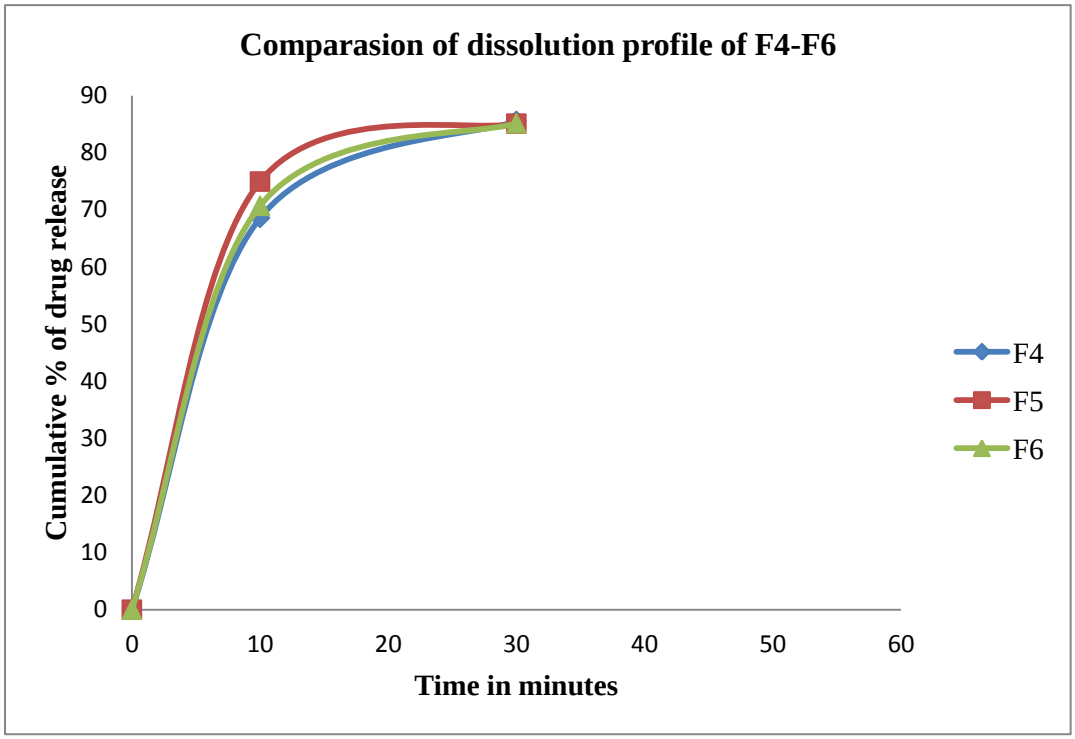
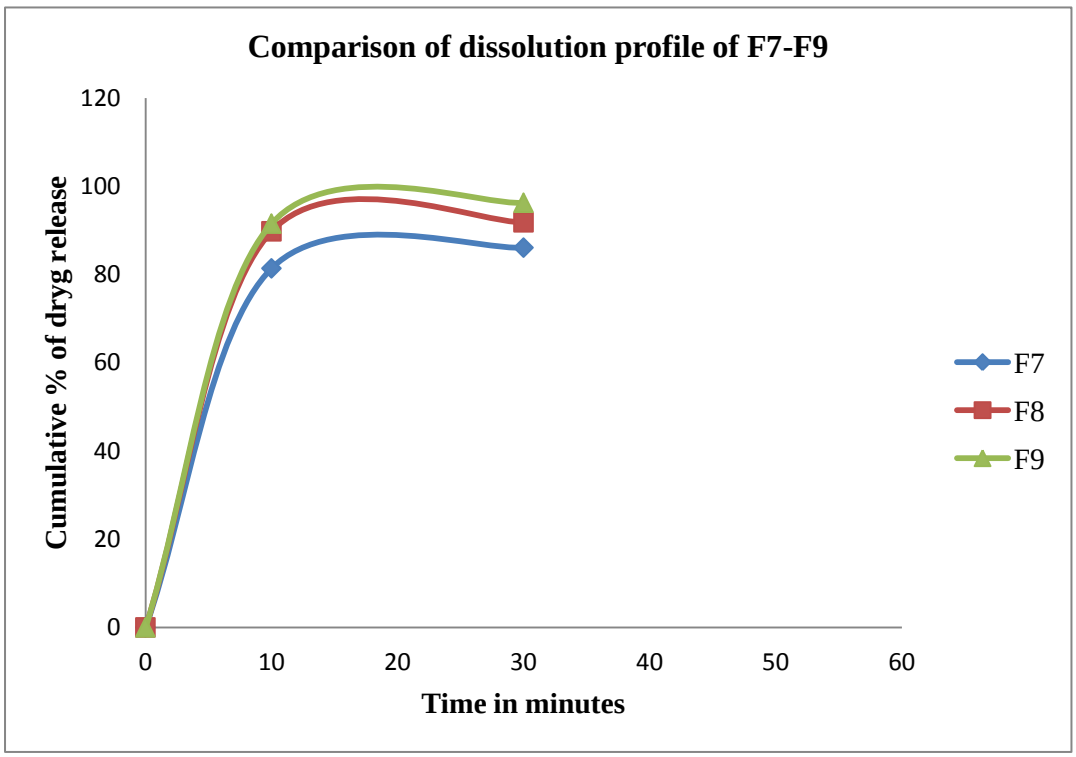


Fig No: 23 Comparison of Dissolution profile of F7-F9



INNOVATOR CHARACTERIZATION:

Name **:** Fexofenadine Hydrochloride Tablet 180mg

Brand Name **:** Allegra

Lot No **:** 1138211

Table No: 22

TEST PARAMETERS	**RESULTS**	
Description	Oval shaped film coated tablet. Orange(peach) colour	
Average weight	653mg	
Hardness	11 - 12 Kg/cm^2	
Thickness	5.80mm	
Disintegration	1'.23''(1 minute and 23 seconds)	
Assay(% label claim)	100	
In-vitro Dissolution study	**Percentage of drug release (%)**	
	10 minutes	30 minutes
	76.02	87.97

EVALUATION OF FEXOFENADINE HYDROCHLORIDE FILM COATED TABLETS

Table No: 23 Evaluation of fexofenadine hydrochloride film

Coated tablets

F. Code	**Thickness (mm)**	**Hardness (kg/cm^2)**	**Weigh variation (mg)**	**Disintegration Time (sec)**		**Assay (%)**	**% of Drug Release (Time in minutes)**	
				With disc	**Without disc**		**10**	**30**
F-9C	5.91±0.13	9.60±0.04	611.89±0.07	48±1.2	39±1.02	100.13	91.06	95.25

COMPARISON OF UNCOATED AND FILM COATED FEXOFENADINE HYDROCHLORIDE TABLETS:

Table No: 24 Comparison of uncoated and film coated fexofenadine Hydrochloride tablets:

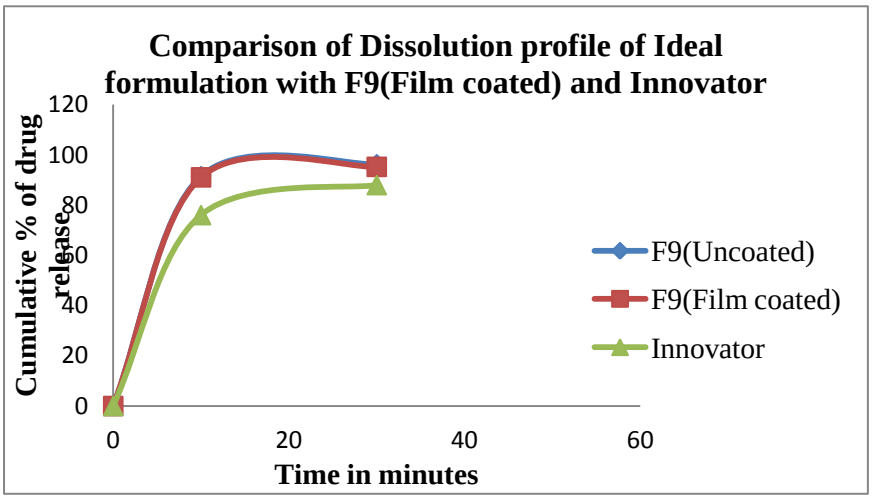
F- code	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Disintegration Time (sec)		Assay (%)	% of Drug release	
				With disc	Without disc		10	30
F-9 (Uncoated)	5.71±0.06	9.5±0.3	599.1 ±1.28	38±1.15	30±1.72	100.7	91.52	96.25
F-9 (Coated)	5.91±0.13	9.6±0.04	611.8 ±0.07	48±1.2	39±1.02	100.1	91.06	95.25

COMPARISON OF DRUG RELEASEOF INNOVATOR PRODUCT WITH F9 (UNCOATED) AND F9 (FILM COATED) TABLET

Table No: 25 Comparison of drug release of innovator product with f9 (uncoated) and f9 (film coated) tablet

S. No.	PRODUCT	% Drug release	
		10 minutes	30 minutes
1	**INNOVATOR PRODUCT**	76.02	87.97
2	**F9 (Uncoated)**	91.52	96.25
3	**F9 (Coated)**	91.06	95.25

Fig No: 23 Comparison of Dissolution profile of ideal formulation with F9 film coated and Innovator product



RESULTS OF STABILITY STUDIES OF F9 FILM COATED TABLETS:

Table No: 26 Results of after stability studies

PARAMETERS		STORAGE CONDITION				
		40^0C±2ºC/75%±5%RH				30^0C±2ºC/ 65%±5%RH
		INITIAL PERIOD	ONE MONTH	TWO MONTHS	THREE MONTHS	THREE MONTHS
Description		Orange (peach), Oval shape tablet	No change	No change	No change	No change
Average weight(mg)		611.89 ±0.07	613.05 ±0.08	613.06 ±0.06	615.03 ±0.05	613.07 ±0.02
DT time (in sec)	with disc	48±1.2	58±1.2	62±1.09	83±1.7	59±1.6
	with out disc	39±1.02	46±1.07	59±2.01	70±1.9	56±1.09
% of drug release	10 mins	91.52	89.53	88.97	88.76	91.12
	30 mins	96.25	94.60	94.58	93.42	95.92
Assay (%)		100.13	98.74	98.71	98.66	99.64

DISCUSSION

Fexofenadine Hydrochloride tablets were formulated by wet granulation method. The prepared uncoated and coated (film) Fexofenadine Hydrochloride tablets were evaluated for the following parameters which includes Hardness, Thickness, Friability, Weight variation test, disintegration test, Assay and *invitro* drug release studies.

Drug Excipients-Compatibility study:

Preformulation compatibility studies were carried out before the formulation. There was no colour change in any of the samples.

The FTIR spectrum of Fexofenadine Hydrochloride shows the presence of peaks at 2934.4 cm^{-1} of C-H stretching (alkane), 1705.4 cm^{-1} of C=O stretching (acid), 1223.2 cm^{-1} of O-H bending (alcohol), and 1552.4 cm^{-1} of N-H group respectively.

The FT-IR spectrum of the combined Fexofenadine Hydrochloride and Microcrystalline cellulose, Pregelatinised starch, Croscarmellose sodium, Colloidal silicon dioxide, and Magnesium stearate shows the presence of peaks at 2922.0 to 2955.6 cm^{-1} of C-H stretching, 1705.1 to 1705.9 cm^{-1} of C=O stretching, 1224.3 cm^{-1} of O-H bending, and 1534.4 to 1577.9 cm^{-1} of N-H group respectively. All the peaks are indicating no interaction between drug and the excipients.

Evaluation of Fexofenadine Hydrochloride granules:

The bulk densities of all formulation were between 0.421 to 0.557 g/ml. The tapped densities of all formulations were between 0.492 to 0.643 g/ml. The Carr's index values ranged from 11.16 to 15.08%. The Hausner's ratio of all formulations ranged from 1.12 to 1.17%. which showed good flow properties.

Tablet characteristics of Fexofenadine Hydrochloride:

Weight variation test:

The weights of the tablets were between 598.8 to 602.25 mg. As the weight of the tablets was 600mg; the acceptable weight variation range is ±5%. As all the tablets meet the official specifications, all the formulations passed the weight variation test.

Thickness and Hardness test:

Thickness of all the formulations was found to be between 5.71 to 5.80 mm respectively and the hardness of all formulations was in the range of 9.5 to 11.5 kg/cm^2 respectively.

Friability test:

The friability values of all formulations was between 0.12 to 0. 28 %, Friability test of all the formulation was found to be within prescribed limits. The results of friability test indicate that the tablets were mechanically stable and could handle the rigors of transportation and handling.

Disintegration test:

Further tablets were subjected for the disintegration test. Disintegration time for all formulations rangedfrom28 to 218 sec. The disintegration time depends on disintegrating agent, method of addition of disintegrant, binder type, it's concentration and force of compression. The formulation (F1-F3) which had starch and lactose showed higher disintegration time compared with the other trials. All the tablets disintegrated within 5 minutes, as all the formulations have super disintegrant between 2-6 %.

Assay:

In all formulations the content of drug were found to be within USP limit (NLT 95.0% and NMT 105.0%).

In-Vitro Dissolution Studies:

The cumulative amount of drug release from all the formulations were found to be 75.67%- 96.25% at the end of 30minutes.

While comparing F1, F2 and F3 it has been observed formulation containing different concentration of excipients was used.

Formulation F1 which has starch (22%), povidone as binder and microcrystalline cellulose (42.66%) as intragranular disintegrant shows cumulative drug release of 75.67% and increased disintegration time.

Formulation F2 which has Starch (20%), Povidone and microcrystalline cellulose (45.83%), has a drug release 76.38% which was same as F1 formulation. The poor release could be attributed to higher binding which is also indicated by the higher disintegration time.

Formulation F3 which has lactose monohydrate (30%) and microcrystalline cellulose (24%& 12%) The lactose monohydrate was added intra granularly and microcrystalline cellulose was added both intra and extra granularly, which showed increase cumulative drug release of80.32%when compared with F1and F2 formulation.

While comparing the release profile of the formulation F4, F5, and F6 it has been observed that all the formulations released above 85% of drug at end of 30 minutes.

Formulation F4 which has microcrystalline cellulose (13% and 20.25%) added both intra and extra granularly and pregelatinised starch (30%) was added intra granularly.

Formulation F5 which has microcrystalline cellulose (20.25%) added intra granularly, microcrystalline cellulose pH 102 (12%) was added extra granularly and pregelatinised starch (30%), was added intra granularly.

Formulation F6 which has microcrystalline cellulose (20.25%) added intra granularly and pregelatinised starch (30% and 12%) was added both intra and extra granularly.

The extra granular addition of the disintegrants has shown faster disintegration time and good dissolution profiles.

Formulation F7 which has microcrystalline cellulose (36.66%)added intra granularly, microcrystalline cellulose pH102 (5%) added extra granularly, and pregelatinised starch (5% and 13%)added both intra and extra granularly showed a drug release was observed 86.07% at end of 30 minutes.

Formulation F8 which has microcrystalline cellulose (20%) added intra granularly, Microcrystalline cellulose pH 102 (11.66%) added extra granularly and pregelatinised starch (20% and 8.3%) was added both intra and extra granularly increased the drug release to91.81% at end of 30 minutes.

In Formulation F9 dissolution profile was improved which has the same concentration of excipients when compared with F8. Only difference being the processing of granules. The granules were dried using a fluidized bed drier in this formulation.

FormulationF1- F9 have been evaluated with respect to hardness, disintegration time, drug release studies, assay and other tests. Based on the above parameters, the trial number F9 showed good results and also it was found to be matching with the innovator product. Considering the above results of F9 it has been selected for further film coating process.

Fexofenadine hydrochloride tablet of the above trial (F9) which satisfied all the parameters was coated using Hydroxypropyl methylcellulose as film polymer in aqueous based solvent by pan coating method. The coated tablets were evaluated for the following parameters including thickness, hardness, weight variation test, disintegration test, and assay and drug release studies.

Comparison study with Innovator product:

The in-vitro dissolution profile of Fexofenadine Hydrochloride batch (F9) was compared with Innovator product. The drug release of formulation (F9) was found to be 91.52 and 96.25 at 10 and 30 minutes respectively. The drug release of innovator product was found to be 76.02 and 87.97 at 10 and 30 minutes respectively. The uncoated tablets shows better release than the innovator product.

After coating:

All the parameters in the evaluation of uncoated tablets were carried out expect friability test for film coated trial (F9C). An increase in 3% weight was observed in film coated tablets when compare to uncoated tablets. The release of film-coated tablets were decreased than uncoated tablets.

Stability studies: The film coated tablet of Fexofenadine Hydrochloride was kept for stability studies at 40^0C±2ºC/75%±5% RH and at 30^0C±2ºC/65%±5% RH.

At 40^0C±2ºC/75%±5% RH, after 3 month period no physical changes were observed. But disintegration time slightly increased. Dissolution and assay datas showed slight variation during stability studies. The three month of accelerated condition results were found to be satisfactory. The results at 30^0C/65% RH after three months showed a slight increase in disintegration time and no significant changes were observed in assay and drug release studies.

10. CONCLUSION

Fexofenadine hydrochloride is a H_1 receptor antagonist and used in urticaria and rhinitis. It is available in market as film coated tablet forms having poor release drug profiles. In this study it was tried to formulate fexofenadine hydrochloride film coated tablet by wet granulation, to improve the drug release profiles.

A total of nine trials of fexofenadine hydrochloride tablets were formulated by wet granulation method. All the trials were evaluated for pre compression and post compression characteristics.

Based on the preliminary studies various formulation trials (F1-F9) were carried out with different concentration of diluents, disintegrants, and binder. From the various formulations, the formulation F9 was finalized as the ideal formula, based on the different parameters which were compared with innovator, which proved to be successful. So it was planned to develop a new fexofenadine hydrochloride film coated tablet by using hydroxypropyl methylcellulose film polymer in aqueous based solvent system and this coated formulation was evaluated for disintegration test, assay, drug release studies and short term stability studies. When subjected to accelerated stability studies the tablet were found to be stable.

Hence stable tablets with an improved drug dissolution profile were suceesfully formulated.

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